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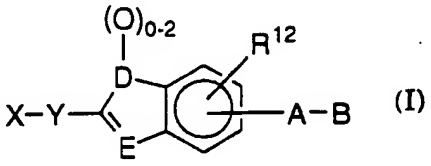

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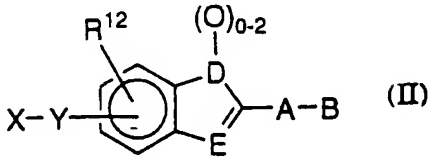

(II)

(57) Abstract

Fibrinogen receptor antagonists of formulae (I) and (II) are disclosed for use in inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets.

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TITLE OF THE INVENTION
FIBRINOGEN RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to the discovery of fibrinogen receptor antagonists of Formula I for use in inhibiting the binding of fibrinogen to blood platelets and inhibiting the aggregation of blood platelets when administered to mammals, preferably humans.

BACKGROUND OF THE INVENTION

The interaction of platelets with the coagulation and fibrinolytic systems in the maintenance of hemostasis may become pathogenic, requiring prevention and treatment. The fibrinogen receptor antagonists of Formula I are useful in treating various diseases related to platelet aggregation and fibrin formation.

An interest in platelet inhibitors has reemerged as a result of a better understanding of the role of platelets and thrombosis in the pathogenesis of vascular disease, including unstable angina, acute myocardial infarction and stroke.

Platelets are cell-like anucleated fragments, found in the blood of all mammals which participate in blood coagulation. Fibrinogen is a glycoprotein present as a normal component of blood plasma. Fibrinogen participates in platelet aggregation and fibrin formation in the blood clotting mechanism. Platelets are deposited at sites of vascular injury where multiple physiological agonists act to initiate platelet aggregation culminating in the formation of a platelet plug to minimize blood loss. If the platelet plug occurs in the lumen of a blood vessel, normal blood flow is impaired.

Platelet membrane receptors are essential in the process of platelet adhesion and aggregation. Interaction of fibrinogen with a receptor on the platelet membrane complex IIb/IIIa is known to be essential for normal platelet function.

Zimmerman et al., U.S. Patent No. 4,683,291, describes peptides having utility in the study of fibrinogen-platelet, platelet-

platelet, and cell-cell interactions. The peptides are described as having utility where it is desirable to retard or prevent formation of a thrombus or clot in the blood.

Pierschbacher et al., U.S. Patent No. 4,589,881, describes the sequence of an 11.5 kDal polypeptide fragment of fibronectin which embodies the cell-attachment-promoting activity of fibronectin.

Ruoslahti et al., U.S. Patent No. 4,614,517, describes tetrapeptides which alter cell-attachment activity of cells to various substrates. Ruoslahti et al., U.S. Patent No. 4,578,079, describes similar tetrapeptides having Ser substituted with Thr or Cys.

Pierschbacher et al., Proc. Natl. Acad. Sci. USA, Vol. 81, pp. 5985-5988, October, 1984, describe variants of the cell recognition site of fibronectin that retain attachment-promoting activity. Pierschbacher et. al. further assayed the cell attachment-promoting activities of a number of structures closely resembling the Arg-Gly-Asp-Ser peptide, and found "that the arginine, glycine, and aspartate residues cannot be replaced even with closely related amino acids, but that several amino acids can replace serine without loss of activity."

Ruoslahti et al., Science, Vol. 238, pp. 491-497, October 23, 1987, discuss cell adhesion proteins. They specifically state that "elucidation of the amino acid sequence of the cell-attachment domain in fibronectin and its duplication with synthetic peptides establish the sequence Arg-Gly-Asp (RGD) as the essential structure recognized by cells in fibronectin."

Cheresh, Proc. Natl. Acad. Sci. USA, Vol. 84, pp. 6471-6475, September 1987, describes the Arg-Gly-Asp-directed adhesion receptor involved in attachment to fibrinogen and the von Willebrand Factor.

Adams et al., U. S. Patent No. 4,857,508, describes tetrapeptides which inhibit platelet aggregation and the formation of a thrombus.

Tjoeng et al., EP 352,249, describe platelet aggregation inhibitors which antagonize interactions between fibrinogen and/or

extracellular matrix proteins and the platelet gpIIb/IIIa receptor, including 8-guanido-octanoyl-Asp-2-(4-methoxyphenyl)ethyl amide.

Alig et al., EP 372,486, describe N-aryl beta-amino acids which inhibit fibrinogen, fibronectin and von Willebrand factor to the blood platelet fibrinogen receptor (glyco-protein IIb/IIIa).

Alig et al., EP 381,033, describe di-aryl or heteroaryl substituted alkanoic acid derivatives of a defined formula which inhibit binding of proteins to their specific receptors on cell surfaces, including fibrinogen.

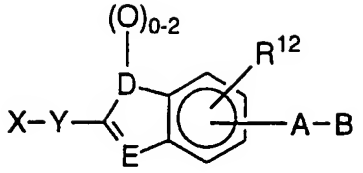
Alig et al., EP 384,362, describe glycine peptides of a specified formula containing an amidine group which inhibit binding of fibrinogen to platelet fibrinogen receptors.

Horwell et al., EP 405,537, describe N-substituted cycloalkyl and polycycloalkyl alpha-substituted Trp-Phe- and phenethylamine derivatives which are useful for treating obesity, hypersecretion of gastric acid in the gut, gastrin-dependent tumors, or as antipsychotics.

It is an object of the present invention to provide fibrinogen receptor antagonists for use in inhibiting the binding of fibrinogen to blood platelets and inhibiting the aggregation of blood platelets. Another aspect of the present invention is to provide novel fibrinogen receptor antagonist compounds. Other objects of the present invention are to provide methods of inhibiting the binding of fibrinogen to blood platelets and inhibiting the aggregation of blood platelets, through the administration of novel fibrinogen receptor antagonist compounds. The above and other objects are accomplished by the present invention in the manner described below.

SUMMARY OF THE INVENTION

The present invention provides fibrinogen receptor antagonist compounds of the formula:



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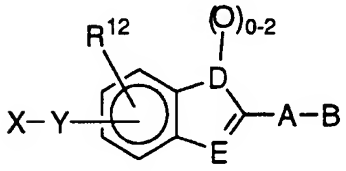


and their pharmaceutically acceptable salts, where D and E are independently chosen from C, N, O, and S;

X is chosen from

$-NR^1R^2$, $-NR^1-\overset{\overset{NR^2}{\|}}{C}-R^1$, $-\overset{\overset{NR^3}{\|}}{C}-NHR^4$,

$-NR^1-\overset{\overset{NR^2}{\|}}{C}-NR^3R^4$, and a 5- to 6- membered mono- or bicyclic aromatic or nonaromatic ring system containing 0, 1, or 2 heteroatoms selected from N, O and S and either unsubstituted or substituted with R^1, R^2, R^3, or R^4, wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen,

C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

Y and A are independently chosen from

$(CH_2)_m$, $(CH_2)_m\overset{O}{\overset{\|}{C}}NR^3(CH_2)_n$, $(CH_2)_mNR^3\overset{O}{\overset{\|}{C}}(CH_2)_n$, $(CH_2)_mO(CH_2)_n$

$(CH_2)_m\overset{O}{\overset{\|}{C}}(CH_2)_n$, $(CH_2)_m\overset{S}{\overset{\|}{C}}(CH_2)_n$, $(CH_2)_mSO_2(CH_2)_n$

$(CH_2)_mS(CH_2)_n$, $(CH_2)_mSO(CH_2)_n$,

$(CH_2)_mSO_2NR^3(CH_2)_n$, $(CH_2)_mNR^3SO_2(CH_2)_n$,

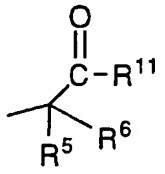
$(CH_2)_m\ CR_3{=}CR_4(CH_2)_n$, $(CH_2)_mC{=}C(CH_2)_n$,

$(CH_2)_m\underset{OH}{CH}(CH_2)_n$, and $(CH_2)_m$aryl$(CH_2)_n$

$(CH_2)_mNR_3(CH_2)_n$

where m and n are integers independently chosen from 0-6;

B is chosen from



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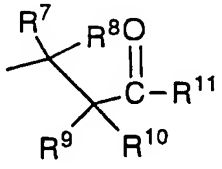

where R^5, R^6, R^7, R^8, R^9, and R^{10} are independently chosen from:

hydrogen, flourine, C_{1-8} alkyl, hydroxyl,
hydroxy C_{1-6} alkyl, carboxy C_{0-6} alkyl,
C_{1-6} alkyloxy,
C_{3-8} cycloalkyl,
aryl C_{0-6} alkyl, C_{1-6} alkylcarbonyloxy,
C_{0-6} alkylamino C_{0-6} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
C_{0-6} dialkylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyloxy,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,

C_{1-6} alkylaminocarbonyloxy,
aryl C_{0-6} alkylaminocarbonyloxy,
aryl C_{0-8} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonyl C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonyl C_{0-6} alkyl,
C_{0-8} alkylaminocarbonyl-amino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl, and
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl,

wherein groups may be unsubstituted or substituted with one or more substituents selected from R^1 and R^2, and

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C-AA where AA is an L- or D- amino acid, or its corresponding ester, connected through an amide linkage;

R^{11} is chosen from:

hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy, and
an L- or D-amino acid joined by an amide linkage

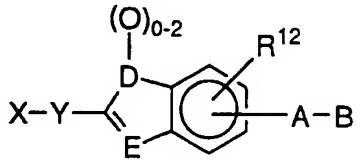
and wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C_{1-6} alkyl; and

R^{12} is chosen from the group described by R^1.

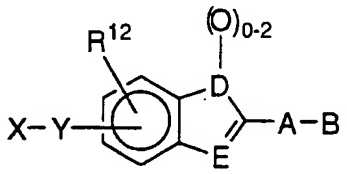
Compounds of the invention are useful for inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets. The above-mentioned compounds can be used in a method of acting upon a fibrinogen receptor which comprises administering a therapeutically effective but non-toxic amount of such compound to a mammal, preferably a human. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, dispersed therein, an effective but non-toxic amount of such compound is another feature of this invention.

DETAILED DESCRIPTION OF THE INVENTION

Fibrinogen receptor antagonist compounds of Formula I are useful in a method of inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets. Fibrinogen receptor antagonists of this invention are illustrated by compounds having the formula:



or



and their pharmaceutically acceptable salts, where D and E are independently chosen from C, N, O, and S;

X is chosen from:

$-NR^1R^2$, $-NR^1-\overset{\overset{NR^2}{\|}}{C}-R^1$, $-\overset{\overset{NR^3}{\|}}{C}-NHR^4$,

$-NR^1-\overset{\overset{NR^2}{\|}}{C}-NR^3R^4$, and a 5- to 6- membered mono- or bicyclic aromatic or nonaromatic ring system containing 0, 1, or 2 heteroatoms selected from N, O, and S and either unsubstituted or substituted with R^1, R^2, R^3, or R^4, wherein R^1, R^2, R^3, and R^4 are independently selected from the group consisting of hydrogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy, and
hydrogen C_{0-6} alkyl;

Y and A are independently chosen from

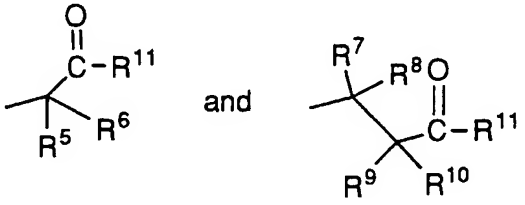
$(CH_2)_m$, $(CH_2)_m\overset{\overset{O}{\|}}{C}NR_3(CH_2)_n$, $(CH_2)_mNR_3\overset{\overset{O}{\|}}{C}(CH_2)_n$, $(CH_2)_mO(CH_2)_n$
$(CH_2)_m\overset{\overset{O}{\|}}{C}(CH_2)_n$, $(CH_2)_m\overset{\overset{S}{\|}}{C}(CH_2)_n$, $(CH_2)_mSO_2(CH_2)_n$
$(CH_2)_mS(CH_2)_n$, $(CH_2)_mSO(CH_2)_n$,
$(CH_2)_mSO_2NR_3(CH_2)_n$,
$(CH_2)_mNR_3SO_2(CH_2)_n$, $(CH_2)_m$ $CR_3{=}CR_4(CH_2)_n$,
$(CH_2)_mC{=}C(CH_2)_n$, $(CH_2)_m$aryl$(CH_2)_n$, $(CH_2)_mNR_3(CH_2)_n$,

OH

$(CH_2)_mCH(CH_2)_n$, and $(CH_2)_mNR_3(CH_2)_n$

where m and n are integers independently chosen from 0-6;

B is chosen from



and their pharmaceutically acceptable salts, where R^5, R^6, R^7, R^8, R^9, and R^{10} are independently chosen from:

hydrogen, flourine,
C_{1-8} alkyl, hydroxyl,
hydroxy C_{1-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-6} alkyloxy, C_{3-8} cycloalkyl,
aryl C_{1-6} alkyloxy,
aryl C_{0-6} alkyl, C_{1-6} alkylcarbonyloxy,
C_{0-6} alkylamino C_{0-6} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyloxy,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8}alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonlyamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,

C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonyl C_{0-6} alkyl, and
aryl C_{0-8} alkylaminocarbonyl C_{0-6} alkyl,

wherein groups may be unsubstituted or substituted with one or more substituents selected from R^1 and R^2; and

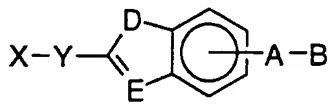
C-AA where AA is an L- or D-amino acid, or its corresponding ester, connected through an amide linkage;

R^{11} is chosen from

hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy, and
an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C_{1-6} alkyl; and

R^{12} is chosen from the group described by R^1.

A preferred embodiment of the present invention are the compounds



and the pharmaceutically acceptable salts, where D and E are independently chosen from O, N, C and S;

X is chosen from

$-NR^1R^2$, $-NR^1-\overset{\overset{NR^2}{\|}}{C}-R^1$, $-\overset{\overset{NR^3}{\|}}{C}-NHR^4$,

$-NR^1-\overset{\overset{NR^2}{\|}}{C}-NR^3R^4$, or a 5- to 6- membered mono- or bicyclic nonaromatic ring system containing 0, 1, or 2 heteroatoms selected from N, O, and S and either unsubstituted or substituted with R^1, R^2, R^3 or R^4, wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of
hydrogen,
C_{1-10} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy, and
hydroxy C_{0-6} alkyl;

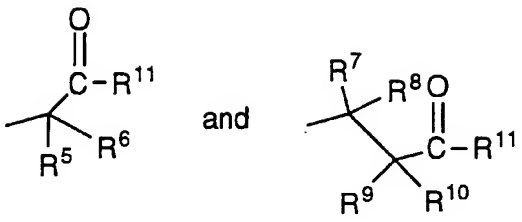
Y and A are independently chosen from

$(CH_2)_m\overset{\overset{O}{\|}}{C}NR_3(CH_2)_n$, $(CH_2)_mNR_3\overset{\overset{O}{\|}}{C}(CH_2)_n$,

$(CH_2)_m$, $(CH_2)_m\overset{\overset{O}{\|}}{C}(CH_2)_n$, $(CH_2)_mO(CH_2)_n$,
$(CH_2)_mS(CH_2)_n$, $(CH_2)_mSO_2NR_3(CH_2)_n$,
$(CH_2)_mCR_3{=}CR_4(CH_2)_n$, and

where m and n are integers independently chosen from 0-6;

B is chosen from



where R^5, R^6, R^7, R^8, R^9, and R^{10} are independently chosen from:

hydrogen, flourine
C_{1-8} alkyl, hydroxyl,
hydroxy C_{1-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-6} alkyloxy, C_{3-8} cycloalkyl,
aryl C_{0-6} alkyl, C_{1-6} alkylcarbonyloxy,
C_{0-6} alkylamino C_{0-6} alkyl, aryl C_{0-6} alkylcarbonyloxy,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
aryl C_{1-6} alkylaminocarbonyloxy,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl

wherein groups may be unsubstituted or substituted with one or more substituents selected form R^1 and R^2; and

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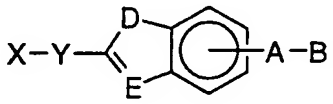
C-AA, where AA is an L- or D-amino acid, or its corresponding ester, connected through an amide linkage; and

R^{11} is chosen from

hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy, and an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C_{1-6} alkyl.

A more preferred embodiment of the present invention are the compounds



where D and E are independently chosen from C, N, O and S;

X is chosen from

NR3
-NR1R2, -C-NHR4, and a 5- to 6- membered mono- or bicyclic nonaromatic ring system containing 0, 1, or 2 heteroatoms selected from N, O and S and either unsubstituted or substituted with R^1, R^2, R^3 or R^4,

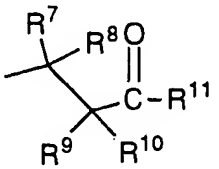
wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen,
C_{1-10} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,

Y and A are optional substituents that are independently chosen from

$(CH_2)_m$, $(CH_2)_m\overset{O}{\overset{\|}{C}}NR_3(CH_2)_n$, $(CH_2)_mNR_3\overset{O}{\overset{\|}{C}}(CH_2)_n$,
$(CH_2)_mO(CH_2)_n$,
$(CH_2)_m\overset{O}{\overset{\|}{C}}(CH_2)_n$, $(CH_2)_mSO_2(CH_2)_n$,
$(CH_2)_mSO_2NR_3(CH_2)_n$,

where m and n are integers independently chosen from 0-6;

B is



where R^7, R^8, R^9, and R^{10} are independently chosen from:

hydrogen, fluorine,
C_{1-8} alkyl, hydroxyl,
hydroxy C_{1-6} alkyl,
carboxy C_{0-6} alkyl C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl,
C_{3-8} cycoalkyl, aryl C_{0-6} alkylcarbonyl, aryl C_{0-6} alkyl,
C_{1-6} alkylcarbonyloxy, C_{0-6} alkylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyoxy,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,

C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl, and
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl; and

R^{11} is chosen from

hydroxy,
C_{1-8} alkyloxy, and
aryl C_{0-6} alkyloxy.

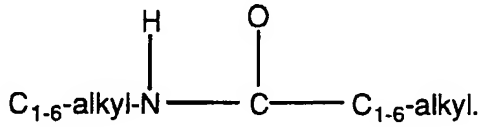
The term "aryl" means a mono- or bicyclic system composed of 5- and 6- membered aromatic rings containing 0, 1, or 2 heteroatoms chosen from N, O or S.

The term "alkyl" means straight or branched alkane, alkene or alkyne. The term "alkoxy" includes an alkyl portion where alkyl is as defined above.

The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and an aryl portion where aryl is as defined above. The C_{0-n} or C_{1-n} designation, where n may be an integer from 1-10 or 2-10 respectively, refers to the alkyl component of the arylalkyl or alkylaryl unit.

The term "halogen" includes fluorine, chlorine, iodine and bromine.

The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom. Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. For example, a C_{1-6} alkyl substituted with C_{1-6} alkylcarbonylamino is equivalent to



Most preferred compounds of the invention, with corresponding IC_{50} values for some of these in parentheses, are:

2-(Butylsulfonylamino)-3-{5[2'-(4-piperidin-4-yl-propyl)benzo-furanyl]}propanoic acid (IC_{50}=0.20 μM);

2-(Butylsulfonylamino)-3-{5-[2'-(4-piperidin-4-yl-methyl)amino-carbonyl]benzofuranyl}propionic acid (IC_{50}=6.6 μM);

2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-N-carbo-benzyloxyaminopropionic acid)carboxamide (IC_{50}=0.067 μM);

2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-N-butyl-sulfonylaminopropionic acid)carboxamide (IC_{50}=0.036 μM);

2-[2-(Piperidin-4-yl)ethyl]benzothiophene-S,S-dioxide-6-N-[3-(2(S)-N-butylsulfonylaminopropionic acid)carboxamide;

2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2-(S)-N-Methylsulfonylaminopropionic acid)]carboxamide;

2-[2-(4-Piperidinyl)ethyl]benzimidazole-5-carbonyl-[2(S)-p-toluenesulfonylamino]-ß-alanine;

2-[2-(4-Piperidinyl)ethyl]benzimidazole-5-carbonyl-[2(S)-butylsulfonylamino]-ß-alanine (IC_{50}=0.022 μM); and

5-[2-[4-Piperidinylethyl)oxy]-2-indolecarbonyl-2(S)-phenylsulfonylamino-ß-alanine (IC_{50}=0.012 μM), and

2-[Z-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2-(S)-benzylureido)propionic acid]carboxamide.

The ADP-stimulated platelet aggregation assay was used to determine IC_{50} inhibition associated with compounds of the invention.

Human platelets were isolated from fresh blood, collected into acid citrate/dextrose by differential centrifugation followed by gel filtration on Sepharose 2B in divalent ion-free Tyrode's buffer (pH 7.4) containing 2% bovine serum albumin. Platelet aggregation was measured at 37°C in a a Chronolog aggregometer. The reaction mixture contained gel-filtered human platelets (2 x 10^8 per l), fibrinogen (100 μg/ml), Ca^{2+} (1 mM), and the compound to be tested. Aggregation was initiated by adding 10 uM ADP 1 minute after the other components had been added. The reaction was allowed to proceed for at least 2 minutes. The extent of inhibition of aggregation was expressed as the percentage of the rate of aggregation observed in the absence of inhibitor. The IC_{50} is the dose of a particular compound inhibiting aggregation by 50% relative to a control lacking the compound.

The abbreviations listed below are defined as Bn, benzyl; NMM, N-methylmorpholine; HOBt, 1-hydroxybenzotriazole; EDC, 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride; DMF, dimethylformamide; Pib, 4-(4-piperidyl)butanoyl; pTSA, para-toluenesulfonic acid; DMS, dimethylsulfide; TFA, trifluoroacetic acid; THF, tetrahydrofuran; DIBAL, diisobutylaluminum hydride; Boc (or BOC), tert-butoxycarbonyl; Cbz, benzyloxycarbonyl; Suc, succinoyl; alpine borane, β-isopinocamphenyl-9-borabicyclo[3.3.1]-nonane; TBDMS, tert-butyldimethylsilyl; Jones reagent, chromic acid; NBS, N-Bromosuccinimide; DEAD, diethyl azodicarboxylate; BPO, Benzoyl peroxide; PPh_3, triphenyl phosphine; DMSO, Dimethylsulfoxide; Et_3N, triethylamine; Tf_2O, triflic anhydride; DMAP, 4-dimethylamino-pyridine; BOP, benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate; PhCHO, benzaldehyde; and Boc_2O, di-t-butyldicarbonate; dppp, 1,3-bis(diphenylphosphino)propane;

$TMSCHN_2$, trimethylsilyl diazomethane; EtOAc, ethyl acetate; CH_2Cl_2, methylene chloride; HOAc, acetic acid; CH_3OH, methanol; $CHCl_3$, chloroform; AA is an L- or D-amino acid chosen from naturally occurring amino acids glycine, alanine, valine, isoleucine, leucine, serine, threonine, proline, aspartic acid, glutamic acid, lysine, arginine, asparagine, glutamine, cysteine, methionine, tryptophan, phenylalanine, tyrosine, and histidine.

Unless otherwise indicated, all degree values are Celsius.

2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl iodide, (3-2), used in Scheme 3, is prepared by according to the following procedure.

4-Piperidine-2-ethanol (Aldrich) (130 g, 1.0 mole) was dissolved in 700 mL dioxane, cooled to 0°C and treated with 3 N NaOH (336 mL, 1.0 mole), and di-t-butyldicarbonate (221.8 g, 1.0 mole). The ice bath was removed and the reaction stirred overnight. The reaction was concentrated, diluted with water and extracted with ether. The ether layers were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to give Boc-4-piperidine-2-ethanol.
R_f = 0.37 in 1:1 EtOAc/Hexanes, ninhydrin stain
^1H NMR (300MHz, $CDCl_3$) δ 4.07 (bs, 2H), 3.7 (bs, 2H), 2.7 (t, J = 12.5 Hz, 2H), 1.8-1.6 (m, 6H), 1.51 (s, 9H), 1.1 (ddd, J = 4.3, 12.5, 12 Hz, 2H).

Boc-4-piperidine-2-ethanol (10.42 g, 0.048 mole was dissolved in 400 ml benzene and imidazole (4.66 g, 0.068 moles) and triphenylphosphine (15.24 g, 0.05 moles) were added at room temperature. After 6 hours the reaction mixture was filtered and the filtrate was evaporated to give a dark residue. This was purified by flash chromatography on silica gel eluting with 10%-EtOAc-hexanes to give Boc-4-piperidine-2-ethyl iodide as a yellow oil.

The alcohol 1-1 is prepared according to Example 18, pages 21-22, up to line 21, of EP 478 328, prior to THF and triphenylphosphine treatment.

The pharmaceutically acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quarternary

ammonium salts of the compounds of Formula I formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acids of Formula I are also readily prepared by conventional procedures such as treating an acid of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

The compounds of Formula I are useful in inhibiting the binding of fibrinogen to blood platelets, inhibiting aggregation of blood platelets, treatment of thrombus formation or embolus formation, and in the prevention of thrombus formation or embolus formation. These compounds are useful as pharmaceutical agents for mammals, especially for humans. The compounds of this invention may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. Compounds of this invention may also be used to prevent or modulate the progress of myocardial infarction, unstable

angina and thrombotic stroke, in either acute or chronic settings. In addition, they may be useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. Compounds of this invention may be administered to surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used for cardiovascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between gpIIb/IIIa on the platelet membranes and fibrinogen adsorbed to the surface of the circuit. (Gluszko et al., Amer. J. Physiol., 1987, 252:H, pp 615-621). Platelets released from artificial surfaces show impaired hemostatic function. Compounds of this invention may be administered to prevent adhesion.

Other applications of these compounds include prevention of platelet thrombosis, thromboembolism, reocclusion, and restenosis during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism, reocclusion and restenosis after angioplasty of coronary and other arteries and after coronary artery bypass procedures.

The compounds of Formula I may be administered to mammals, preferably in combination with pharmaceutically-acceptable carriers or diluents, optionally with known adjuvants such as alum, in a pharmaceutical composition which is non-toxic and in a therapeutically effective amount, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including intravenous, intramuscular, intraperitoneal, trans-dermal, subcutaneous and topical administration.

For oral use of a fibrinogen receptor antagonist according to this invention, the selected compounds may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are

commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added.

For intramuscular, intraperitoneal, subcutaneous, and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The present invention also encompasses a pharmaceutical composition useful in the treatment and prevention of diseases related to platelet aggregation, fibrin formation, and thrombus and embolus formation, comprising the administration of a therapeutically effective but non-toxic amount of the compounds of Formula I, with or without pharmaceutically acceptable carriers or diluents.

Compositions of this invention include fibrinogen receptor antagonist compounds of this invention in combination with pharmacologically acceptable carriers, e.g. saline, at a pH level e.g. 7.4, suitable for achieving inhibition of platelet aggregation. The compositions may also be combined with anticoagulants such as heparin or warfarin. The compositions may also be combined with thrombolytic agents such as plasminogen activators or streptokinase in order to inhibit platelet aggregation in more acute settings. The composition may further be combined with antiplatelet agents such as aspirin. The compositions are soluble in an aqueous medium, and may therefore be effectively administered in solution.

When a compound according to Formula I is used as a fibrinogen receptor antagonist in a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patients symptoms.

In one exemplary application, a suitable amount of compound is administered orally to a heart attack victim subsequent to angioplasty. Administration occurs subsequent to angioplasty, and is in an amount sufficient to inhibit platelet aggregation, e.g. an amount which achieves a steady state plasma concentration of between about 0.01-100 μM preferably between about 0.1-50 μM.

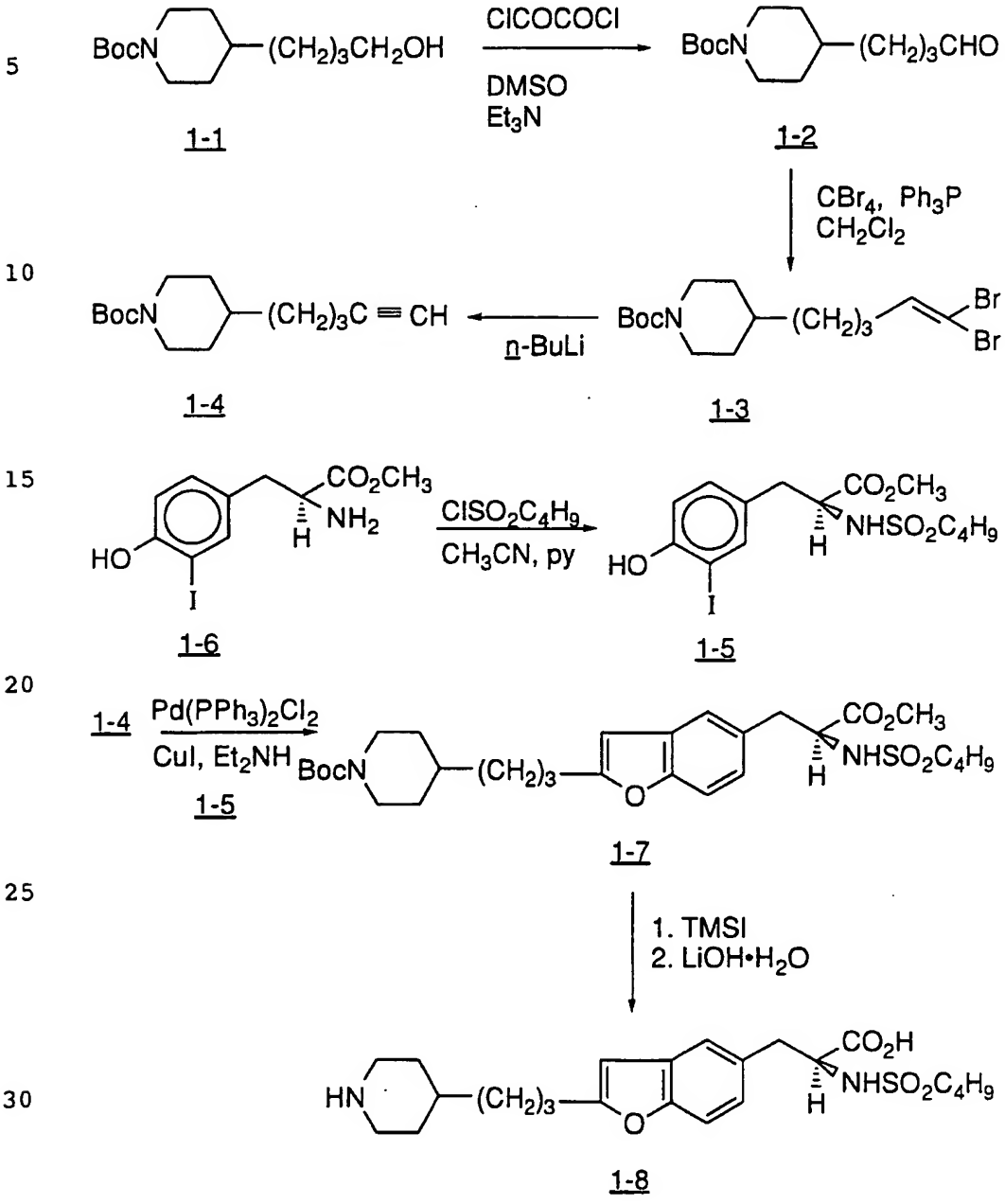
The present invention also includes a pharmaceutical composition comprising compounds of the present invention in combination with tissue type plasminogen activator or streptokinase. The invention also includes a method for promoting thrombolysis and preventing reocclusion in a patient which comprises administering to the patient an effective amount of compositions of the invention.

The present invention provides a method of inhibiting the binding of fibrinogen to blood platelets, inhibiting aggregation of blood platelets, treating thrombus formation or embolus formation, and in preventing thrombus formation or embolus formation in a mammal, comprising the administration of a therapeutically effective but non-toxic amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents.

The present invention still further provides a method of inhibiting the binding of fibrinogen to blood platelets, inhibiting aggregation of blood platelets, treating thrombus formation or embolus formation, and in preventing thrombus formation or embolus formation in a mammal, comprising the administration of a therapeutically effective but non-toxic amount of the compounds of this invention in combination with thrombolytic agents, such as tissue plasminogen activators or streptokinase, anticoagulants such as heparin or warfarin, or antiplatelet agents such as aspirin, with or without pharmaceutically acceptable carriers or diluents.

The compounds of Formula I are prepared according to the reaction schemes set forth below.

SCHEME I


BocN
(CH2)3CH2OH
ClCOCOCl
DMSO
Et3N
(CH2)3CHO
1-1
1-2
CBr4, Ph3P
CH2Cl2
(CH2)3C ≡ CH
n-BuLi
(CH2)3
Br
Br
1-4
1-3
CO2CH3
NH2
H
HO
I
ClSO2C4H9
CH3CN, py
NHSO2C4H9
1-6
1-5
1-4
Pd(PPh3)2Cl2
CuI, Et2NH
1-5
O
1-7
1. TMSI
2. LiOH•H2O
CO2H
HN
1-8

4-(N-t-Butyloxycarbonylpiperidin-4-yl)butanal(1-2)

A solution of oxalyl chloride (8.48 moles) in CH_2Cl_2 (60 ml) cooled to -70° was treated with DMSO (11.27 mmoles) and this was stirred for 15 min. A solution of 1-1 (1.45g, 5.63 mmoles) was added and the resulting mixture stirred for 2 hrs at -70°. Then, triethylamine (28.7 mmoles) was added and the reaction mixture was stirred for 2.0 hrs.

The reaction mixture was washed in H_2O, 10% $KHSO_4$ solution, H_2O, brine and dried (Na_2SO_4). Solvent removal gave 1-2 as an oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H,m), 1.23 - 1.40 (4H,m), 1.45 (9H,s), 1.58 - 1.74 (4H,m), 2.43 (2H,dt), 2.68 (2H,dt), 4.09 (2H,bd), 9.78 (1H,s).

5-(N-t-Butyloxycarbonylpiperidin-4-yl)-1,1-dibromo-pent-1-ene (1-3)

A solution of CBr_4 (3.45g, 10.42 mmol) in CH_2Cl_2 (40 ml) was cooled to 0° and treated with Ph_3P (5.46g, 20.8 mmol) with stirring for 1.5 hrs. Reaction mixture was then cooled to -70° and treated with 1-2 (1.29g, 5.08 mmol) in CH_2Cl_2 (10 ml) and this was stirred for 0.5 hr.

The reaction was then quenched with Et_3N (4 ml), warmed to room temperature and poured into hexane (500 ml). The suspension was filtered and the filtrate concentrated to provide a residue that was purified by flash chromatography on silica gel eluting with hexane (15)/EtOAc (1) to give pure 1-3.

^1H NMR (300 MH_Z, $CDCl_3$) δ 1.08 (2H,m), 1.20 - 1.40 (4H,m), 1.45 (9H,s), 1.62 (2H,bd), 2.08 (2H,m), 2.67 (2H,t), 4.06 (2H,d), 6.39 (1H,t).

5-(N-t-Butyloxycarbonylpiperidin-4-yl)pent-1-yne (1-4)

A solution of 1-3 (1.70g, 4.13 mmol) in THF (80 ml) was cooled to -78° and treated with n-BuLi (4.25 mmol) with stirring for 15 min. The reaction was then quenched with 10% $KHSO_4$ (25 ml) and the solvent was removed. The residue was taken up in Et_2O (150 ml) and this was washed with 10% $KHSO_4$ solution, brine, and dried (Na_2SO_4).

Solvent removal gave 1-4 as an oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H,m), 1.20 - 1.40 (4H,m), 1.47 (9H,s), 1.55 (1H,m), 1.64 (2H,bd), 2.08 (1H,q), 2.20 (1H,dt), 2.68 (2H,dt), 4.08 (2H, bd), 6.39 (1H,t).

Methyl 2(S)-(Butylsulfonylamino)-3-(4-hydroxy-3-iodo)-phenyl-propionate (1-5)

A solution of 1-6 (3-iodo-L-tyrosine (Aldrich) was converted to 1-6 by treatment with $SOCl_2$/MeOH in the normal fashion) (10.5g, 0.033 mol) in CH_3CN (150 ml) was treated with pyridine (0.039 mol) and butanesulfonyl chloride (0.039 mmol) and the resulting mixture was heated at 60° for 2 days.

The solvent was removed and the residue was taken up in 10% $KHSO_4$ soln and extracted with EtOAc. The organic extract was dried and the solvent removed to give 1-5.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H,t), 1.35 (1H,m), 1.61 (2H,m), 2.78 (2H,m), 2.89 (1H,m), 3.08 (1H,dd), 3.78 (3H,s), 4.29 (1H,m), 5.10 (1H,m), 5.98 (1H,m) 6.89 (1H,d), 7.08 (1H,d), 7.50 (1H,m).

Methyl 2(S)-(Butylsulfonylamino)-3-{5-[2'-3-(N-t-butyloxycarbonyl-piperidin-4-ylpropyl)benzofuranyl]}-proionate (1-7)

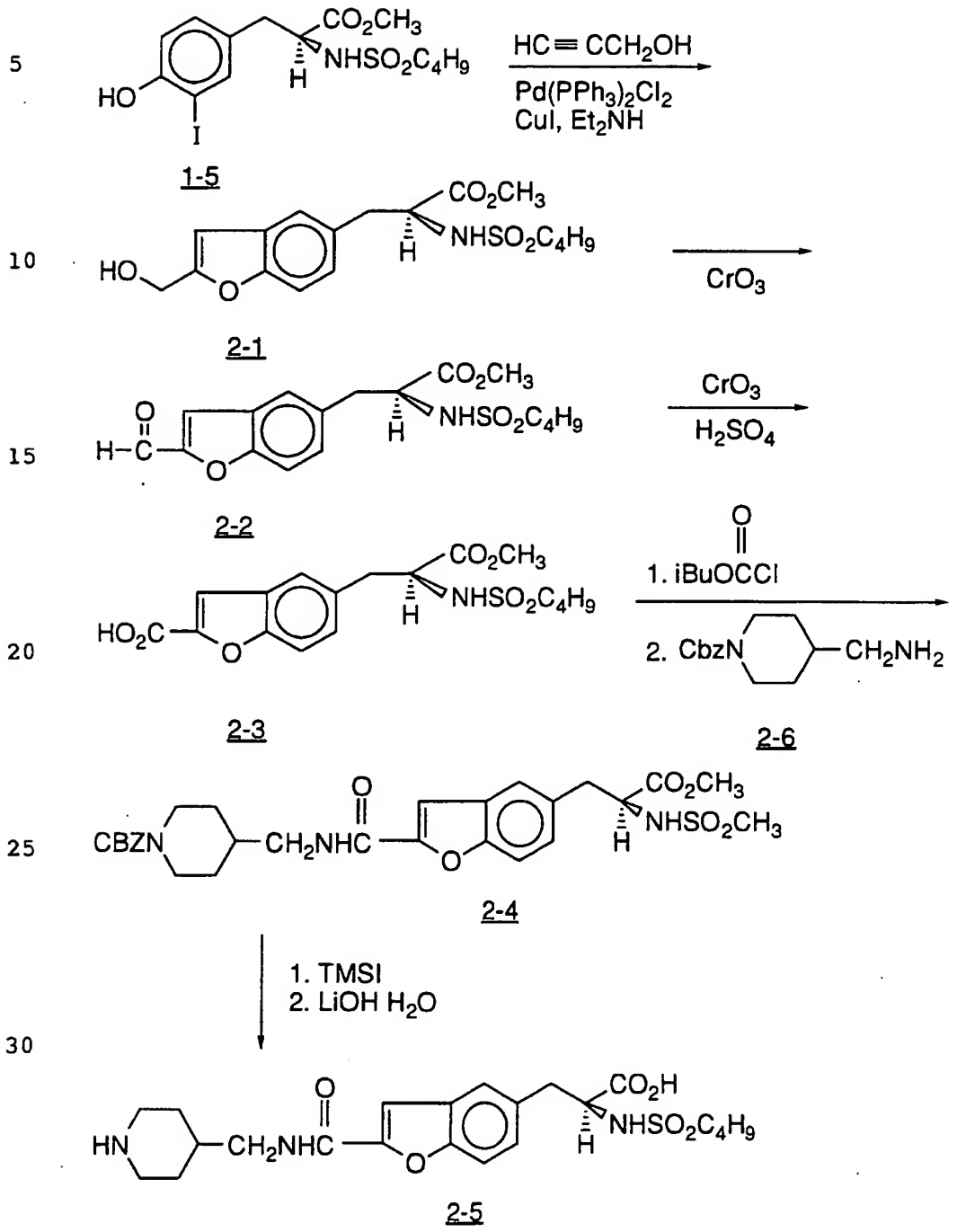
A solution of 1-5 (0.485.g, 1.14 mmol) in diethylamine (10 ml) was treated with Pd $(Ph_3P)_2Cl_2$ (0.04g), cuprous iodide (5.5 mg) and 1.4 (0.34g, 1.37 mmol) and the resulting mixture was stirred at rt for 72 hrs.

The solvent was removed and the residue purified by flash chromatography in silica gel eluting with hexane (80)/EtOAc (20) to give pure 1-7.
^{1}H NMR (300 MH_Z, $CDCl_3$) δ 0.77 (t,J=7.3Hz, 3H), 1.05 - 1.42 (m, 9H), 1.44 (s, 9H), 1.48 - 1.77 (m,4H), 2.68 (m, 6H), 3.04 (dd,J=7.6, 13.8 Hz, 1H), 3.23 (dd,J=5.1, 13.8 Hz, 1H), 3.77 (s, 3H), 4.07 (bs, 2H), 4.35 (dd,J=5.1, 7.6 Hz, 1H), 4.5 (bs, 1H), 6.32 (s, 1H), 6.98 (m, 1H), 7.25 (m, 3H).

2(S)-(Butylsulfonylamino)-3-{5-[2'-3-(piperidin-4-ylpropyl)benzofuranyl]}propionic acid (1-8)

A solution of 1-7 (0.18g, 0.33 mmol) in $CHCl_3$ (20 ml) was treated with TMSI at room temperature. After 15 minutes 10 ml CH_3OH was added, and the solvent was then removed. The residue was taken up in THF (1)/MeOH (1)/H_2O (1) (12 ml/and $LiOH \cdot H_2O$ (0.138g, 3.28 mmol) was added. After 2 hours at room temperature the solvent was removed and the residue was purified by flash chromatography on silica gel eluting with EtOH(9)/NH_4OH(1)/H_2O(1) to give pure 1-8. ^1H NMR (300 MH_Z, CD_3OD) δ 0.78 (t,J=7.3 Hz, 3H), 1.06 - 1.6 (m, 10H), 1.78 (m,2H), 1.85 (bd, J = 14.5 Hz, 2H), 2.68 (m, 2H), 2.75 (m,2H), 2.85 (m, 2H), 2.90 (dd, J = 8.3, 13.6Hz, 1H), 3.20 (dd, J = 4.8, 13.6 Hz, 1H), 3.30 (m, 2H), 3.97 (dd, J = 4.8, 8.3 Hz, 1H), 6.41 (s, 1H), 7.16 (dd, J = 1.8, 8.1 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H) 7.4 (d, J= 1.7 Hz, 1H).

SCHEME 2


CO2CH3
NHSO2C4H9
HO
I
H
HC≡CCH2OH
Pd(PPh3)2Cl2
CuI, Et2NH
1-5
CrO3
2-1
H-C=O
CrO3
H2SO4
2-2
HO2C
1. iBuOCCl
2. CbzN
CH2NH2
2-3
2-6
CBZN
CH2NHC
NHSO2CH3
2-4
1. TMSI
2. LiOH H2O
HN
CO2H
2-5

Methyl 2(S)-(Butylsulfonylamino)-3-{5-[2'-(hydroxymethyl)]-benzofuranyl}propionate (2-1)

Propargyl alcohol (2.05 mmol) was dissolved in Et_2NH (5 ml) and treated with 1-5 (0.83g, 1.95 mmol), $Pd(PPh_3)_2Cl_2$ (0.060g) and CuI (0.009g) and the resulting mixture was stirred at room temperature for 4 days. The solvent was removed and the residue purified by flash chromatography on silica gel eluting with hexane (6)/EtOAc(4) to give pure 2-1.
^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (3H,t), 1.23 (2H,m), 2.58 (2H,m), 2.00 (1H,m), 2.71 (2H,t), 3.03 - 3.30 (2H,m), 3.77 (3H,s), 4.40 (1H,m), 6.60 (1H,s), 7.07 (1H,d), 7.38 (2H,m).

Methyl 2(S)-(Butylsulfonylamino)-3-{5-[2'-(formyl)-benzofuranyl]}-propionate (2-2)

A solution of 2-1 (0.050g, 0.0135 mmol) in CH_2Cl_2 (50 ml) was treated at room temperature with CrO_3/pyridine (0.081 mmol CrO_3 in 10 ml CH_2Cl_2 containing 0.63 pyridine). After 1.0 hour the solvent was removed and the residue purified by flash chromatography on silica gel eluting with hexane (1)/EtOAc (1) to give pure 2-2.
^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (3H,t), 1.23 (2H,m), 1.57 (2H,m), 2.77 (2H,m), 3.21 (2H,m), 3.79 (3H,s), 4.40 (1H,m), 5.02 (1H,m), 7.35 (1H,dd), 7.58 (3H,m), 9.87 (1H,s),

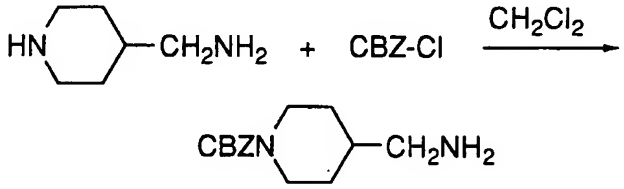
Methyl 2(S)-(Butylsulfonylamino)-3-{5-[2'-(carboxy)benzofuranyl]}-propionate (2-3)

A solution of 2-2 (0.135g, 0.0367 mmol) in acetone (10 ml) was treated with CrO_3/H_2SO_4 reagent dropwise. After 10 minutes the orange color had disappeared and the reaction was greenish. After 0.5 hr saturated $NaHCO_3$ soln was added to pH=9 and this was extracted in EtOAc. The aqueous phase was then acidified to pH 2-3 with 10% $KHSO_4$ solution and extracted with EtOAc. The organic extract was dried (Na_2SO_4) and the solvent removed to give 2-3.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H,t), 1.33 (2H,m), 1.70 (2H,m), 2.93 (2H,m), 3.26 (2H,m), 3.84 (3H,s), 4.55 (1H,bs), 5.75 (1H,bs), 7.22 (1H,m), 7.40 (1H,bs), 7.52 (2H,bs).

Methyl 2(S)-(Butylsulfonylamino)-3-{5-[2'-(4-N-carbobenzyloxy-piperidinylmethyl)aminocarbonyl]benzofuranyl}propionate (2-4)

A solution of 2-3 (0.11g, 0.29 mmol) in CH_2Cl_2 (10 ml) was cooled to 0° and treated with N-methylmorpholine (0.057 mmol) followed by isobutyl chloroformate (0.032 mmol). After stirring at 0° for 10 minutes N-CBZ-(4-aminomethyl)piperidine (2-6) (0.078g, 0.032 mmoles) was added and reaction was stirred for 1.0 hr. The reaction mixture was quenched with pH 7 buffer and extracted with CH_2Cl_2. The organic phase was washed with 10% $KHSO_4$, brine, dried (Na_2SO_4) and the solvent was removed to provide 2-4.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (3H,t), 1.23 (4H,m), 1.58 (2H,m), 1.80 (3H,m), 2.75 (4H,m), 3.07 - 3.30 (2H,m), 3.57 (2H,m) 3.76 (3H,s) 4.22 (2H,m), 4.38 (1H,m), 4.96 (1H,d), 5.10 (1H,s) 6.75 (1H,t), 7.21 - 7.50 (9H,m).



2-6

N-CBZ-(4-Aminomethyl)piperidine (2-6)

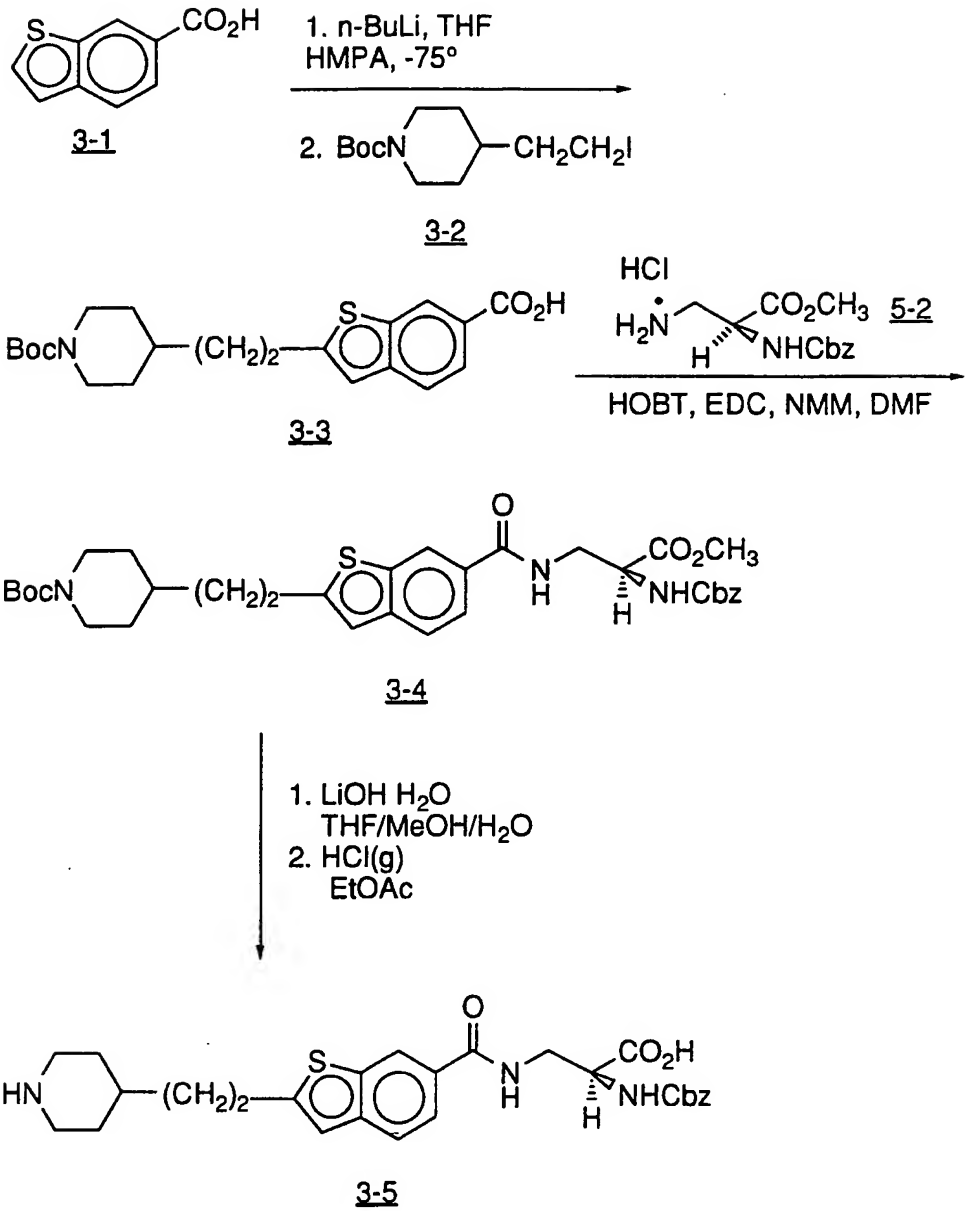
A solution of 4-(aminomethyl)piperidine (Aldrich) (5.0 g, 0.0438 mol) in CH_2Cl_2 (100 ml) was cooled to -78° and treated with CBZ-Cl (Aldrich) (0.022 mol) dropwise. The reaction mixture was stirred at -78°C for 0.5 hr and then allowed to warm to 0° over 1 hour. The reaction mixture was filtered and the solution concentrated to give

a residue that was purified by flash chromatography on silica gel eluting with 5% MeOH/$CHCl_3$ + 1% Et_3N to give pure 2-6.
^1H NMR (300 MHz, $CDCl_3$) δ 1.1 (2H, m), 1.4 (3H, m), 1.7 (2H, bd), 2.57 (2H, d), 2.75 (2H, bt), 4.2 (2H, bs), 5.11 (2H, s), 7.2-7.4 (5H, m).

2(S)-(Butylsulfonylamino)-3-{5-[2'-(4-piperidinylmethyl)amino-carbonyl]benzofuranyl}propionic acid (2-5)

A soln of 2-4 (0.13g, 0.21 mmol) in CH_2Cl_2 (10 ml) was treated with TMSI (2.5 mmol) at room temperature for 0.5 hr. Methanol (5 ml) was then added with stirring and the solvent was removed. The residue was taken up in THF (1)/MeOH (1)/H_2O(1) (12 ml) and LiOH•H_2O (0.088g, 2.1 mmol) was added. After stirring for 1.0 hr. at room temperature the solvent was removed and the residue was purified by flash chromatography on silica gel eluting with EtOH(1)/H_2O (1)/MeOH (1) to give pure 2-5.
^1H NMR (300 MHz, CD_3OD) δ 0.82 (t, J = 7.3Hz, 3H), 1.26 ((m, 2H), 1.4 - 1.6 (m, 4H), 2.0 (bd, 14.5Hz, 3H), 2.8 (m, 2H), 3.0 (m, 3H), 3.20 (m, 1H), 3.3 - 3.5 (m, 4H), 3.99 (dd, J = 4.8, 7.9Hz, 1H), 7.3 - 7.5 (m, 3H), 7.6 (s, 1H).

SCHEME 3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HMPA, -75°
2. BocN
CH2CH2I
3-1
3-2
HCl
CO2CH3
5-2
NHCbz
HOBT, EDC, NMM, DMF
BocN
(CH2)2
CO2H
3-3
3-4
1. LiOH H2O
THF/MeOH/H2O
2. HCl(g)
EtOAc
HN
3-5

2-[2-(n-t-Butyloxycarbonylpiperidin-4-yl)ethyl]benzothiophene-6-carboxylic acid (3-3)

A solution of benzothiophene-6-carboxylic acid (1.78g, 0.01 mol) in THF (140 ml) cooled to -75° was treated with n-BuLi (0.02 mol) dropwise and the resulting solution was stirred at -70° for 1 hr. Then, a solution of 2-(N-t-Butyloxycarbonylpiperidin- 4-yl)ethyl iodide (3.39g, 0.01 mol) in THF (10 ml) was added dropwise followed by HMPA (1.79g, 0.01 mol). The resulting solution was stirred at -70° for 4 hrs and then at 23° for 16 hrs. The cooled reaction was quenched with 10% $KHSO_4$, the solvent removed, and the residue was taken up in H_2O (150 ml) and extracted with EtOAc. The solvent was removed and the residue was purified by flash chromatography on silica gel eluting with $CHCl_3$(97)/MeOH (2)/HOAC (1) to give a solid which was identified to be a mixture of 3-1 and 3-3.

These were separated to by a sequence that involved conversion to the methyl ester, column chromatography [(silica, hexane(4)/EtOAC (1)], and hydrolysis ($LiOH \cdot H_2O$) to give pure 3-3. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, m), 1.42 (9H, s), 1.50 (2H, m), 1.72 (4H, m) 2.68 (2H, m), 2.97 (2H, m, 4.12 (2H, m), 7.09 (1H, s), 7.72 (1H, d), 8.05 (1H, d).

2-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]benzothiophene-6-N-[3-(methyl 2(S)-N-carbobenzyloxyaminopropionate)]carboxamide (3-4)

A solution of 3-3 (0.44g, 0.0011 mol), 5-2 (0.329g, 0.0014 mol), and HOBT (0.17g, 0.0012 mol) in DMF (20 ml) at ambient temperature was treated with N-methylmorpholine (NMM), (0.34g, 0.0034 mol) followed by EDC (0.25g, 0.0013 mol). After stirring overnight, the solvent was removed and the residue was taken up in EtOAc (200 ml) and washed with 10% $KHSO_4$ solution, brine, saturated $NaHCO_3$ solution and dried ($NaSO_4$). The solvent was removed and the residue purified by flash chromatography on silica gel eluting with hexane(55)/EtOAc(45) to give pure 3-4 as a solid.

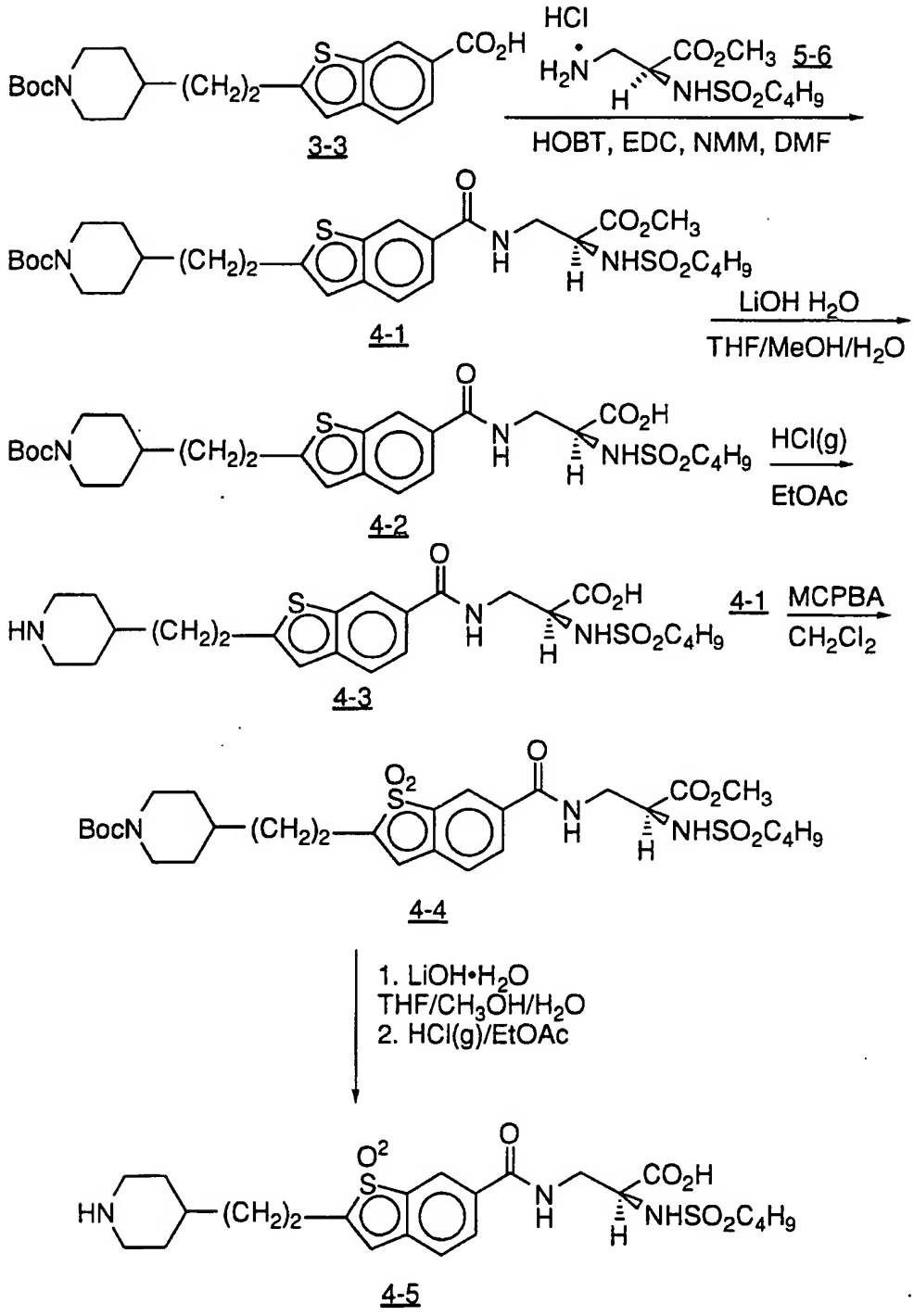
R_f 0.35, silica, hexane(1)/EtOAc(1)

^{1}H NMR (300 MHz, $CDCl_3$) 1.20 (2H,m), 1.43 (9H,s), 1.50 (2,H,m), 1.73 (4H, m), 2.75 (2H,bt), 2.95 (2H,t), 3.78 (2H,s), 3.89 (2H,m), 4.08 (2H,m), 4.56 (1H,m), 5.11 (2H,s), 5.96 (1H,d), 7.03 (1H,s), 7.31 (2H,m), 7.63 (1H,m).

2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-N-carbobenzyloxyaminopropionic acid)]carboxamide (3-5)

A solution of 3-4 (0.12g, 0.19 mmol) in THF (1)/MeOH (1)/H_2O (1) (10 ml) was treated at 23° with $LiOH \cdot H_2O$ (0.024g, 0.58 mmol) for 18 hrs. The solvent was removed and the residue was taken up in H_2O (50 ml), acified to pH 2-3 with 10% $KHSO_4$ soln, and extracted with EtOAc. The extract was dried (Na_2SO_4), the solvent removed, and the residue purified by flash chromatography on silica gel eluting with $CHCl_3$(95)/MeOH(5)/HOAC (1) to give the desired acid, R_f 0.25 (silica, $CHCl_3$(95)/MeOH(5)/HOAC (1). This acid was dissolved in EtOAc (25 ml), cooled to -25° and treated with HCl (g) for 15 min and then stirred at 0° for 1 hr. The solvent was removed and the residue was trituated with EtOAc to give pure 3-5. R_f 0.3 [(silica, EtOH(9)/H_2O(1)/NH_4OH (1)].

SCHEME 4


HCl
BocN
(CH2)2
S
CO2H
3-3
H2N
CO2CH3
5-6
H
NHSO2C4H9
HOBT, EDC, NMM, DMF
O
N
H
4-1
LiOH H2O
THF/MeOH/H2O
4-2
HCl(g)
EtOAc
HN
4-3
4-1
MCPBA
CH2Cl2
O2
4-4
1. LiOH•H2O
THF/CH3OH/H2O
2. HCl(g)/EtOAc
4-5

2-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]benzothiophene-6-N-[3-(Methyl 2(S)-butylsulfonylaminopropionate)]carboxamide (4-1)

A solution of 3-3 (0.58g, 0.0015 mol), 5-6 (0.41g, 0.0015 mol) and HOBT (0.22g, 0.0016 mol) in DMF (20 ml) was treated at room temperature with NMM (0.45g, 0.0045 mol) followed by EDC (0.34g, 0.00175 mol) and the resulting mxt. was stirred for 16 hrs.

The solvent was removed, and the residue was diluted with H_2O (150 ml) and extracted with EtOAc. The organic extract was washed with 10% $KHSO_4$ solution, brine, saturated $NaHCO_3$ solution and dried ($NaSO_4$). Solvent removal provided a residue that was purified by flash chromatography on silica gel eluting with $CHCl_3$(98)/ MeOH (2) to give pure 4-1. R_f 0.25, silica, $CHCl_3$(98)/MeOH (2).
^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t), 1.18 (2H, m), 1.39 (2H, t), 1.45 (9H, s), 1.50 (2H, m), 1.58 - 1.85 (6H, m), 2.67 (2H, bt), 2.95 (2H, t), 3.03 (2H, m), 3.83 (3H,s), 3.92 (1H, m), 4.09 (2H, m), 4.36 (1H, m), 5.63 (1H, d), 6.85 (1H, t), 7.02 (1H, s), 7.68 (1H, s), 8.25 (1H, s).

2-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-butylsulfonylaminopropionic acid)]carboxamide (4-2)

4-1 (0.054g, 0.0031 mol) was treated with $LiOH \cdot H_2O$ as described for 2-5 to give 4-2. R_f 0.2, silica, $CHCl_3$(95)/MeOH (5).

2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-butylsulfonylaminopropionic acid)]carboxamide (4-3)

4-2 (0.23g) was dissolved in EtOAc and treated with HCl (g) as described for 3-6 to give 4-3, R_f 0.3, silica, EtOH(9)/H_2O(1)/ NH_4OH(1)
^1H NMR (300 MHz, CD_3OD) δ 0.87 (3H, t), 1.38 (4H, m), 1.75 (5H, m), 2.02 (3H, m), 3.00 (6H, m), 3.38 (2H, bd), 3.60 (1H, m), 3.85 (1H, dd), 4.34 (1H, m), 7.18 (1H, s), 7.77 (2H, m), 8.30 (1H, s).

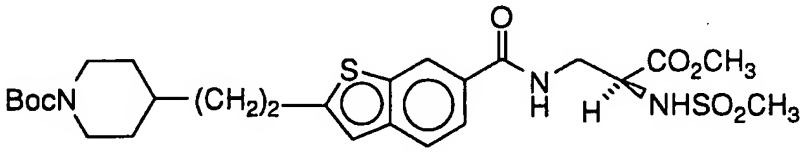
2-[2-(N-t-Butyloxcarbonylpiperidin-4-yl)ethyl]benzothiophene-S,S-dioxide-6-N-[3-(Methyl 2(S)-butylsulfonylaminopropionate)]-carboxamide (4-4)

A solution of m-chloroperbenzoic acid (0.216g, 0.001 mol) in CH_2Cl_2 (10 ml) at room temperature was treated with 4-1 (0.24g, 0.4 mmol) and the resulting solution was stirred for 3 hrs. This was diluted with CH_2Cl_2 (100 ml), washed with H_2O, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). The solvent was removed and the residue purified by chromatography on silica gel eluting with hexane(35)/EtOAc(65) to give 4-4, Rf 0.35, silica, hexane(35)/EtOAc (65).

2-[2-(Piperidin-4-yl)ethyl]benzothiophene-S,S-dioxide-6-N-[3-(2(S)-N-butylsulfonylaminopropionic acid)]carboxamide (4-5)

4-4 (0.25g, 0.39 mmol) was treated with $LiOH \cdot H_2O$ as described for 3-5 to provide the desired acid, Rf 0.3, silica, $CHCl_3$(90)/CH_3OH(9)/HOAc(1). This acid was dissolved in EtOAc and treated with HCl (g) as described for 3-6 to give 4-5, Rf 0.25 [(silica, EtOH(10)/NH_4OH(1)/H_2O (1)].

^1H NMR (300 MHz, CD_3OD) δ 0.76 (3H, t), 1.23 (1H, t), 1.40 (4H, m), 1.78 (5H, m), 2.03 (2H, m), 2.67 (2H, t), 3.04 (4H, m), 3.40 (1H, db), 3.61 (1H, m), 4.09 (1H, m), 4.26 (1H, m), 7.18 (1H, s), 7.55 (1H, d), 8.10 (1H, dd), 8.16 (1H, d).

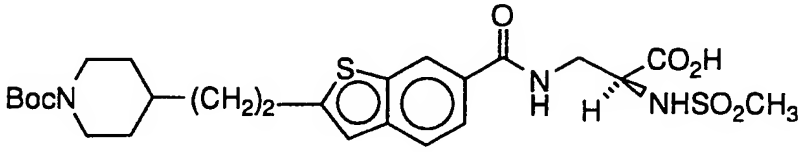


4-6

2-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]benzothiophene-6-N-(3-[methyl 2(S)-N-methylsulfonylaminopropionate)]carboxamide (4-6)

3-3 (0.234g, 0.6 mmol) as treated with 5-7 (0.14g, 0.6 mmol) as described for 4-2 to provide crude 4-6 which was purified by flash chromatography on silica gel eluting with hexane(60)/acetone(40) to provide pure 4-6. Rf 0.4, silica, hexane(60)/acetone (40).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (2H, m), 1.28 (1H, m), 1.45 (9H, s), 1.73 (4H, m), 2.68 (2H, bt), 2.93 (2H, t), 3.00 (3H, s), 3.82 (3H, s), 3.95 (1H, m), 4.08 (2H, m), 4.39 (1H, m), 5.82 (1H, d), 6.87 (1H, t), 7.02 (1H, s), 7.68 (2H, s), 8.23 (1H, s).

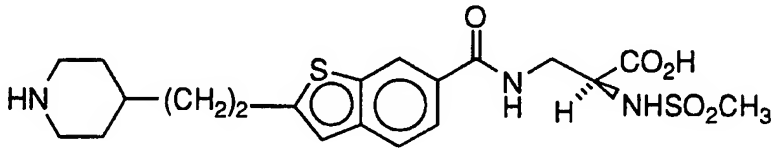


4-7

2-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-methylsulfonylaminopropionic acid)]carboxamide (4-7)

4-6 (0.24g, 0.42 mmol) was treated with $LiOH \cdot H_2O$ (0.053g, 1.27 mmol) as described for 4-1 to provide pure 4-7. R_f 0.2, silica, $CHCl_3$(95)/MeOH (5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (2H, m), 1.45 (9H, s), 1.64 (4H, m), 2.63 (2H, bt), 2.89 (2H, m), 2.91 (3H, s), 3.80 (1H, m), 3.90 (1H, m), 4.07 (2H, m), 4.36 (1H, m), 6.22 (1H, m), 6.95 (1H, s), 7.40 (1H, m), 7.60 (1H, d), 7.66 (1H, d), 8.20 (1H, s).



4-8

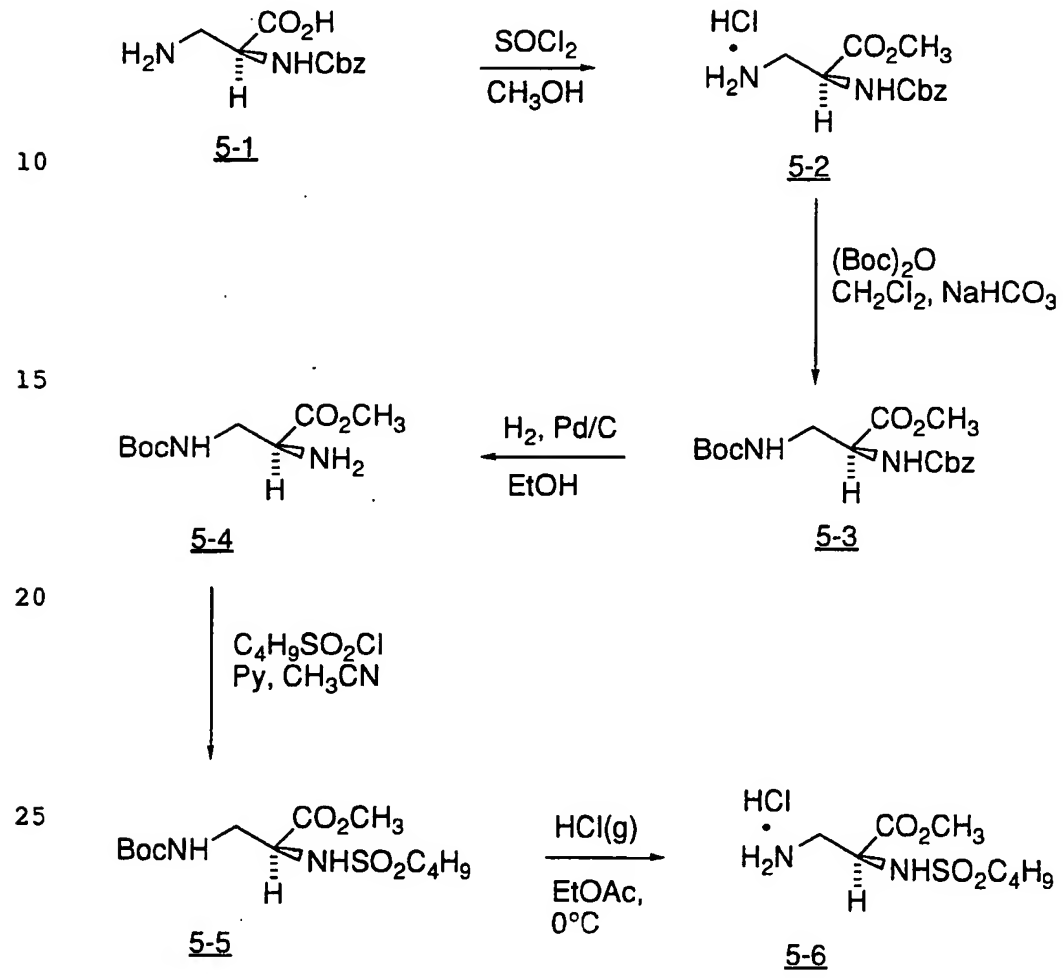
2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-methylsulfonyl-aminopropionic acid)]carboxamide (4-8)

4-7 (0.21g, 3.79 mmol) was dissolved in EtOAc (25 ml) and treated with HCl (g) at -25° as described for 4-3 to give pure 4-8. R_f 0.45, silica, EtOH(10)/conc NH_4OH(1)/H_2O(1).

Calc. for $C_{20}H_{27}N_3O_5S_2$•HCl: C, 49.02; H, 5.76; N, 8.57.
Found: C, 48.73; H, 6.00; N, 8.27.

SCHEME 5

2-Substituted-3-Aminopropionates are prepared in the following manner:



Methyl 2(S)-benzyloxycarbonylamino-3-aminopropionatehydrochloride (5-2)

To a cooled suspension of 2(S)-benzyloxycarbonylamino-3-aminopropionic (Fluka) acid (5-1) (10g, 0.042 mol) in 150 ml of methanol was added 5.47 g (0.046 mol) of thionyl chloride over 20 minutes. The resulting solution was allowed to stir at room temperature overnight. After ~18 hrs, the solvent was removed in vacuo, and the residual solid was stirred with 150 ml of ether for 0.5 hr. The resulting white solid was collected and air dried to give 5-2.

^{1}H NMR (300 MHz, CD_3OD) δ 3.26 (2H, m), 3.45 (1H, dd), 3.77 (3H, s), 4.25 (1H, m), 5.13 (2H, s), 7.37 (5H, m).

Methyl 2(S)-benzyloxycarbonylamino-3-(N-t-butyloxycarbonyl)-aminopropionate (5-3)

To a 2-phase mixture of CH_2Cl_2 (500 ml) and saturated $NaHCO_3$ solution (300 ml) was added 28.87 g (0.10 mol) of 5-2. After a few minutes, 21.83 g (0.10 mol) of di-t-butyldicarbonate was added in one portion and the resulting mixture was stirred at room temperature for 4 hrs. The CH_2Cl_2 layer was then separated from the aqueous layer, and the aqueous layer was extracted with 300 ml of CH_2Cl_2. The combined organic extracts were washed with brine, dried and the solvent removed in vacuo to provide the product as a viscous oil. Trituration of this oil with 300 ml of hexane gave 5-3 as a white solid, m.p. 85°-87°.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H, s), 1.50 (4H, m), 1.62 (1H, m), 3.52 (2H, m), 3.75 (3H, s), 4.41 (1H, m), 4.83 (1H, m), 5.12 (2H, s), 5.78 (1H, m), 7.35 (5H, m).

Methyl 2(S)-amino-3-(N-t-butyloxycarbonyl)aminopropionate (5-4)

To a solution of 6.60 g (0.0187 mol) 5-3 in 150 ml EtOH was added 0.5 g of 10% Pd/C. The resulting mixture was hydrogenated under balloon pressure at r.t. for 4 hrs. The catalyst was filtered off and the solvent removed in vacuo to provide 5-4 as a viscous oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.49 (2H, m), 1.59 (2H, m), 3.25 (1H, m), 3.49 (1H, m), 3.58 (1H,m), 3.75 (3H, s), 5.03 (1H, m)

Methyl 2(S)-butylsulfonylamino-3-(N-t-butylcarbonyl)aminopropionate (5-5)

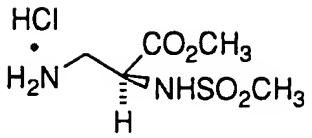
To a solution of 0.400 g (0.00183 mol) of 5-4 in 10 ml of CH_3CN was added 0.226 g (0.00286 mol) pyridine followed by 0.408 g (0.0026 mol) of n-butanesulfonyl chloride. The resulting solution was stirred at room temperature for 2.5 hrs at which time starting material was consumed. The solvent was removed in vacuo and 50 ml of H_2O added to the residual material. This mixture was extracted with 3 x 50 ml portions of ethyl acetate and the combined extracts washed with brine, dried (Na_2SO_4), filtered and concentrated to give 0.5 g of a viscous oil. Trituration to this oil with 25 ml of hexane provided 5-5 as a white, amorphous solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, t), 1.43 (9H, s), 1.48 (2H, m), 1.80 (2H, m), 3.03 (2H, m), 3.52 (2H, t), 3.80 (3H, s), 4.22 (1H, m), 4.99 (1H, bt), 5.48 (1H, bd),

Methyl 2(S)-butylsulfonylamino-3-aminopropionatehydrochloride (5-6)

A cooled (-20°C) solution of 0.400 g (0.00118 mol) of 5-5 in 25 ml of ethyl acetate was treated with HCl gas for 15 min. The resulting solution was then stoppered and allowed to stir at 0°C for an additional hour. The solvent and excess HCl were removed in vacuo to give 5-6 as a hygroscopic, yellowish foam.

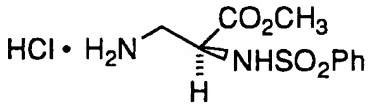
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t), 1.44 (9H, s), 1.48 (2H, m), 1.80 (2H, m), 3.04 (2H, m), 3.53 (2H, bt), 3.80 (3H, s), 4.22 (1H, m), 4.93 (1H, m), 5.40 (1H, bd).



5-7

Methyl 2(S)-Methylsulfonylamino-3-aminopropionatehydrochloride (5-7)

5-7 was prepared as described above for the butyl-sulfonylamino analog (5-6) using methanesulfonyl chloride at the appropriate stage.
^{1}H NMR (300 MHz, CD_3OD) δ 3.07 (3H, s), 3.13 (1H, m), 3.43 (1H, dd), 3.83 (3H, s), 4.96 (1H, m).

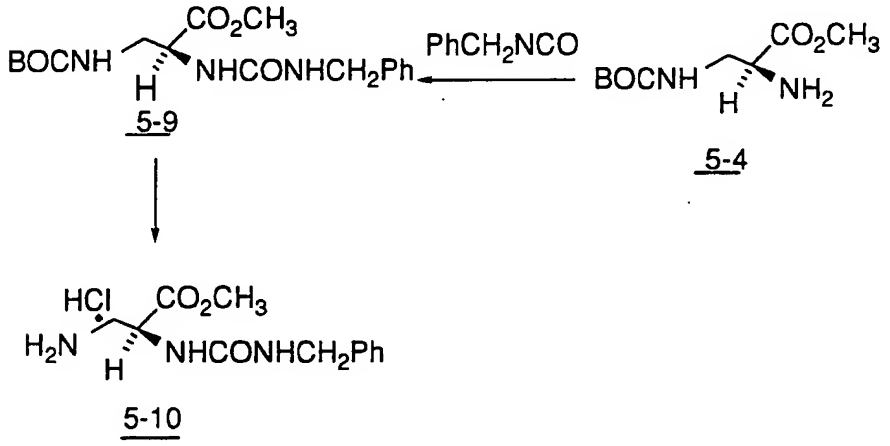


5-8

Methyl 2(S)-Phenylsulfonylamino-3-aminopropionate hydrochloride (5-8)

5-8 was prepared as described above for 5-6 using phenylsulfonylchloride at the appropriate stage.
^{1}H NMR (300 MHz, D_2O) δ 3.22 (1H, t), 3.45 (3H, S), 3.51 (2H, m), 4.44 (1H, m), 7.61-7.80 (3H, m), 7.92 (2H, m).

2(S)-Benzylureido-3-aminopropionic acid methyl ester hydrochloride (5-10)



5-9 5-4 5-10

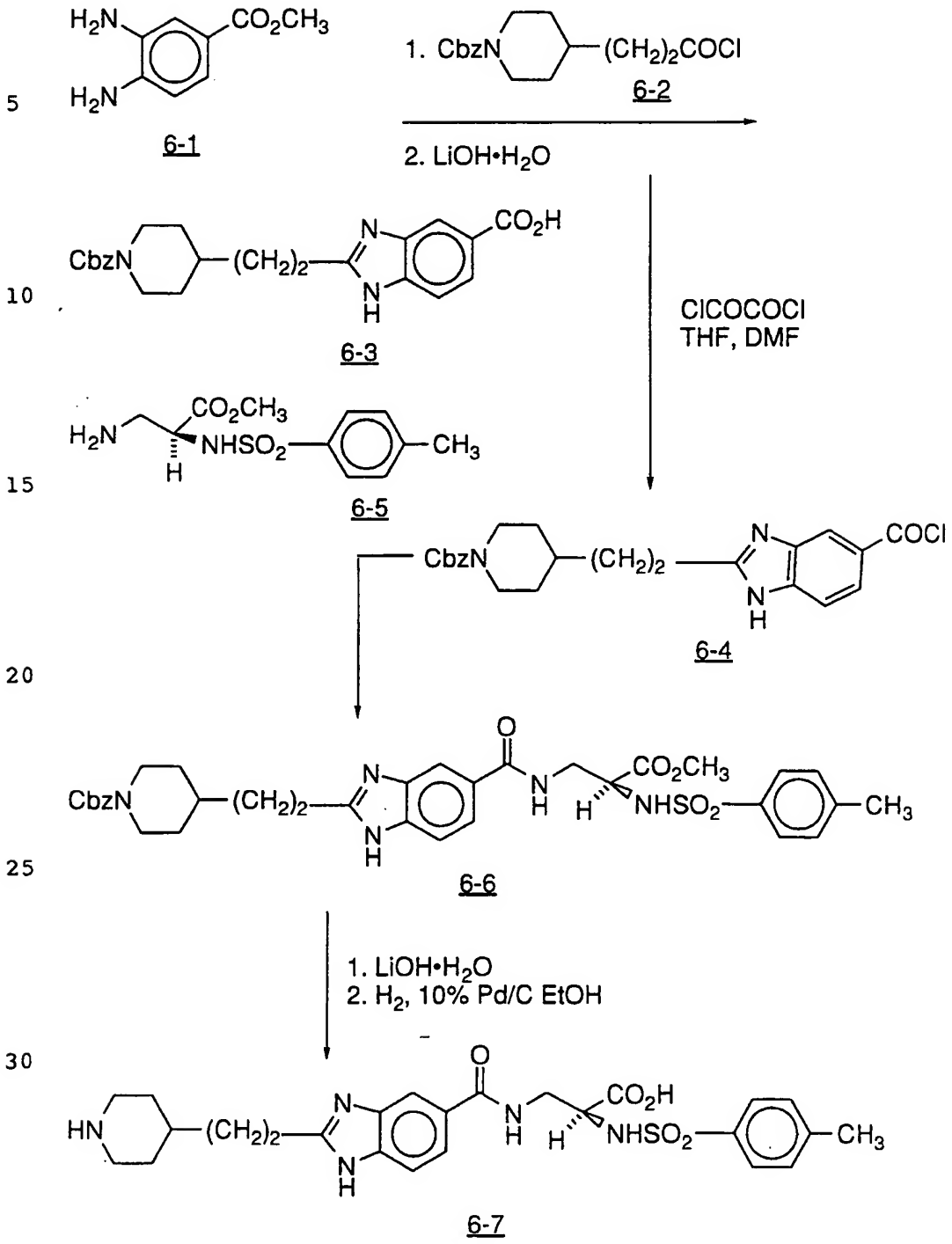
2(S)-Benzylureido-3-(N-t-butyloxycarbonyl)aminopropionic acid methyl ester (5-9)

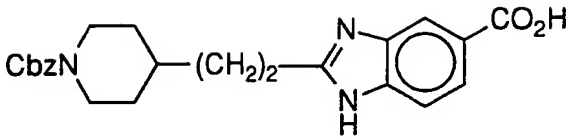
A solution of 5-4 (1.29 g, 5.9 mmoles) in THF (35 ml) was treated with benzylisocyanate (6.5 mmoles) at room temperature. After stirring for 16 hours, the solvent was removed and the residue was purified by flash chromatography on silica gel eluting with 5% MeOH/EtOAc to give 5-9. Rf 0.7 (silica, 10% MeOH/EtOAc)
^{1}H NMR (300 MHz, CD_3OD) δ 1.45 (9H, s), 3.41 (1H, m), 3.53 (1H, m), 3.62 (3H, s), 3.70 (1H, s), 4.32 (3H, m), 5.27 (1H, m), 5.45 (1H, m), 5.90 (1H, m).

2(S)-Benzylureido-3-aminopropionic acid methyl ester hydrochloride (5-10)

Treatment of 5-9 (1.91 g) with HCl gas in EtOAc as described for 5-5 provided pure 5-10. Rf 0.66 (silica, 5% MeOH/$CHCl_3$/NH_3)
^{1}H NMR (300 MHz, CD_3OD) δ 3.25 (1H, dd) 3.45 (1H, dd), 3.8 (3H, S), 4.4 (2H, S), 4.6 (1H, dd), 7.4 (5H, m).

SCHEME 6


H2N
CO2CH3
H2N
6-1
1. CbzN
(CH2)2COCl
6-2
2. LiOH•H2O
CbzN
(CH2)2
N
N
H
CO2H
6-3
ClCOCOCl
THF, DMF
H2N
CO2CH3
NHSO2
CH3
H
6-5
CbzN
(CH2)2
N
N
H
COCl
6-4
CbzN
(CH2)2
O
N
H
CO2CH3
H
NHSO2
CH3
6-6
1. LiOH•H2O
2. H2, 10% Pd/C EtOH
HN
(CH2)2
O
N
H
CO2H
H
NHSO2
CH3
6-7

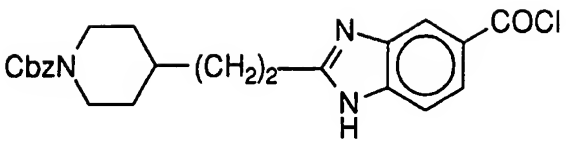


6-3

2-[2-(4-N-CBz-Piperidinyl)ethyl]benzimidazole-5-carboxylic acid (6-3)

A solution of methyl-3,4-diaminobenzoate (6.23 g, 37.5 mmol) in 200 ml toluene containing 80 ml of anhydrous pyridine was heated at reflux and a solution containing 3-(4-N-Cbz-Piperidinyl)-propionyl-chloride 6-2 (2.90 g, 9.35 mmol) in 60 ml of toluene was added dropwise over 30 minutes. The resulting mixture was refluxed for 20 hours then cooled and evaporated. The residue was redissolved in 500 ml CH_2Cl_2, washed successively with 1N HCl (3 x 50 ml), H_2O (100 ml), saturated $NaHCO_3$(1 x 100 ml) and brine, then dried over Na_2SO_4 filtered and evaporated. This yellow residue was chromatographed on silica gel using 3:1 ethyl acetate/hexane to give the desired ester.
^1H NMR ($CDCl_3$) δ 8.25 (s, 1H); 7.95 (d, 1H); 7.55 (d, 1H); 7.36 (m, 5H); 5.17 (s, 2H); 4.18 (d, 2H); 3.93 (s, 3H); 2.92 (t, 2H); 2.76 (m, 2H); 1.79 (m, 2H); 1.68 (d, 2H); 1.50 (m, 1H); 1.13 (m, 2H).

This ester (1.68 g, 4.0 mmol) was dissolved in 15 ml THF and treated with $LiOH \cdot H_2O$ (185 g, 4.4 mmol) in 10 ml H_2O. The resulting solution was stirred at room temperature for 3.5 hours and then the THF was evaporated at reduced pressure and the aqueous residue acidified with 3N HCl. The resulting oily precipitate was washed twice with H_2O then dissolved in 200 ml EtOAc containing 50 ml CH_3OH, dried over Na_2SO_4, filtered and evaporated to give 6-3.
^1H NMR (DMSO-d_6) δ 8.35 (s, 1H); 7.97 (d, 1H); 7.55 (d, 1H); 7.36 (m, 5H); 5.10 (s, 2H); 4.14 (d, 2H); 3.97 (s, 3H); 2.92 (t, 2H); 2.75 (m, 2H); 1.80 (m, 2H); 1.67 (d, 2H); 1.50 (m, 1H); 1.12 (m, 2H).

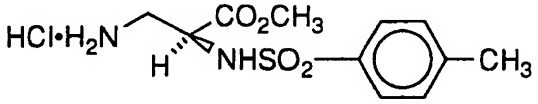


6-4

2-[2-(4-N-Cbz-Piperidinyl)ethyl]benzimidazole-5-carbonyl chloride (6-4)

Acid 6-3 (1.5 g, 3.7 mmol) was suspended in 100 ml of THF and 10 µl DMF was added followed by 25 ml of oxalyl chloride. The resulting clear solution was refluxed under N_2 for 2.5 hours, then cooled and evaporated. The resulting yellow powder was triturated with hexane, filtered, washed with 50 ml of hexane and dried under vacuum to give 6-4.

^{1}H NMR (DMSO-d6) δ 8.53 (s, 1H); 7.93 (d, 1H); 7.57 (d, 1H); 7.36 (m, 5H); 5.18 (s, 2H); 4.18 (d, 2H); 2.93 (t, 2H); 2.81 (m, 2H); 1.82 (m, 2H); 1.68 (d, 2H); 1.50 (m, 1H); 1.13 (m, 2H).

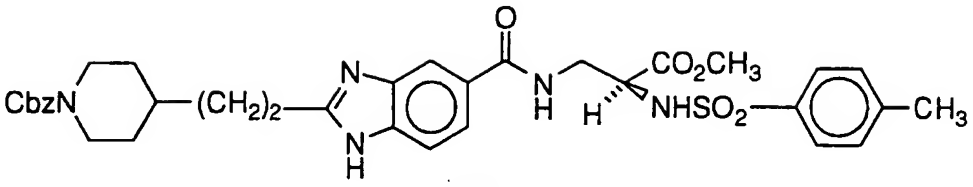


6-5

Methyl-2(S)-Toulenesulfonylamino-3-aminopropionate hydrochloride (6-5)

6-5 was prepared as described above for 5-6 using toluene sulfonyl chloride at the appropriate stage.

^{1}H NMR (300 MHz, DMSO-d6) δ 7.73 (d, 2H), 7.19 (d, 2H), 6.13 (d, 1H); 4.53 (m, 1H); 3.73 (s, 3H); 2.76 (m, 2H); 2.26 (s, 3H).

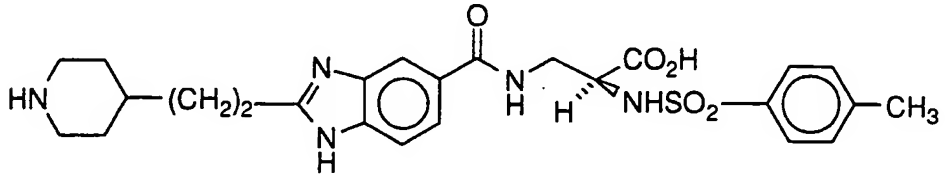


6-6

2-[2-(4-N-Cbz-Piperidinyl)ethyl]benzimidazole-5-carbonyl-[2(S)-p-toluenesulfonylamino]-β-alanine methyl ester (6-6)

The acid chloride (329 mg, 0.78 mmol) was dissolved in 15 ml of THF along with 2(S)-toluenesulfonamino-β-alanine methyl ester hydrochloride (6-5) (238 mg, 0.78 mmol). N-methyl morpholine (215 µl, 1.94 mmol) was added and the resulting solution was stirred under N_2 for 3.5 h after which the solvent was removed at reduced pressure. The residue was redissolved in 100 ml CH_2C1_2 and washed with 10% $KHSO_4$ (50 ml) then H_2O (50 ml), dried over Na_2SO_4 and concentrated. This crude material was purified by flash chromatography on silica using 5% CH_3OH/EtOAc as eluent to give pure 6-6.

^1H NMR ($CDCl_3$) δ 8.15 (br s, 1H); 8.06 (s, 1H); 7.75 (d, 2H); 7.62 (d, 1H); 7.45 (d, 1H); 7.36 (m, 6H); 7.18 (d, 2H); 5.10 (s, 2H); 4.18 (overlapping m, 3H); 3.82 (m, 2H); 3,64 (s, 3H); 3.01 (t, 2H); 2.76 (m, 2H); 2.28 (s, 3H); 1.79 (m, 2H); 1.68 (d, 2H); 1.50 (m, 1H); 1.13 (m, 2H).



6-7

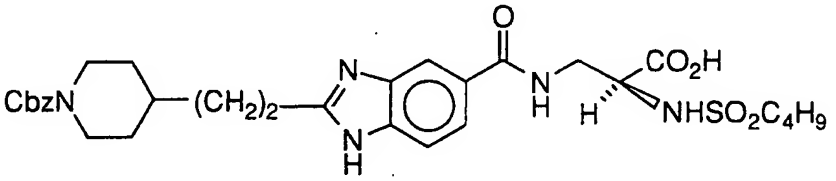
2-[2-(4-Piperidinyl)ethyl]benzimidazole-5-carbonyl[2(S)-p-toluenesulfonylamino]-β-alanine (6-7)

Ester 6-6 (180 mg, 0.273 mmol) was dissolved in 20 ml 50% aqueous THF and treated with $LiOH \cdot H_2O$ (12.56 mg, 0.30 mmol) at room temperature for 2.5 h. Then the organic solvent was evaporated at reduced pressure and the aqueous residue was acidified with 1N HCl and extracted with ethyl acetate (2 x 50 ml). The combined organic phases were dried (Na_2SO_4), filtered and evaporated to give the desired acid.

^1H NMR (CD_3OD) δ 8.13 (s, 1H); 7.85 (d, 1H); 7.72 (d, 1H); 7.62 (d, 2H); 7.32 (m, 5H); 7.18 (d, 2H); 5.14 (s, 2H); 4.21 (overlapping m, 3H); 3.82 (m, 1H); 3.62 (m, 1H); 3.13 (t, 2H); 2.82 (m, 2H); 2.28 (s, 3H); 1.79 (m, 2H); 1.71 (d, 2H); 1.55 (m, 1H); 1.13 (m, 2H).

This acid (167 mg, .0.258 mmol) was dissolved in 10 ml of absolute ethanol, treated with 20 mg 10% Pd on C, and the mixture was stirred under a H_2 filled balloon for 16 h. Next, the catalyst was removed by filtration through Celite and the filtrate evaporated to give pure 6-7, mp 180-185° (dec.).

^1H NMR (DMSO-d_6) δ 8.15 (br s, 1H); 8.06 (s, 1H); 7.75 (d, 2H); 7.62 (d, 1H); 7.45 (d, 1H); 7.18 (d, 2H); 4.18 (overlapping m, 3H); 3.82 (m, 2H); 3.64 (s, 3H); 3.01 (t, 2H); 2.76 (m, 2H); 2.28 (s, 3H); 1.79 (m, 2H); 1.68 (d, 2H); 1.50 (m, 1H); 1.13 (m, 2H)

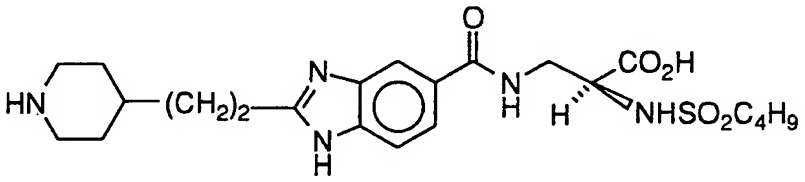


6-8

2-[2-(4-N-Cbz-Piperidinyl)ethyl]benzimidazole-5-carbonyl-[2(S)-butylsulfonylamino]-β-alanine (6-8)

Treatment of 6-4 with 5-6 as described for 6-6 provided the desired ester which was hydrolyzed with $LiOH \cdot H_2O$, as described for 6-7, to give 6-8.

^1H NMR (CD_3OD) δ 8.08 (s, 1H); 7.75 (d, 1H); 7.53 (d, 1H); 7.36 (m, 6H); 5.10 (s, 2H); 4.20-4.09 (overlapping multiplets, 5H); 3.82 (dd, 1H); 3.62 (dd, 1H); 3.06 (t, 2H); 2.96 (t, 2H); 2.78 (m, 2H); 1.821.62 (overlapping multiplets, 6H); 1.50 (m, 1H); 1.38 (m, 2H); 1.13 (m, 2H); 0.85 (t, 3H).

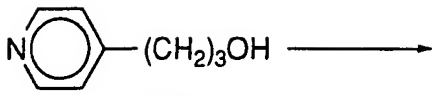


6-9

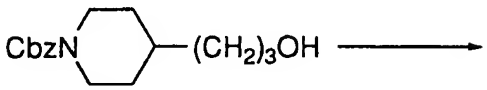
2-[2-(4-Piperidinyl)ethyl]benzimidazole-5-carbonyl-[2(S)-butylsulfonylaminol-ß-alanine (6-9)

6-8 (153 mg, 0.256 mmol) was dissolved in 10 ml of absolute ethanol treated with 20 mg 10% Pd on C and mixture stirred under a H_2 filled balloon for 16.5 h. Next, the catalyst was removed by filtration through Celite and the filtrate evaporated giving a colorless glass which was vacuum dried over P_2O_5 at 50°C to give pure 6-9, mp 180-185°.

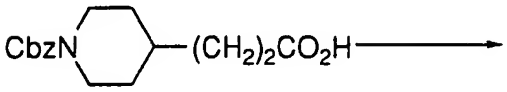
^1H NMR (CD_3OD) δ 8.12 (s, 1H); 7.73 (d, 1H); 7.52 (d, 1H); 4.18-4.09 (overlapping multiplets, 3H); 3.81 (dd, 1H); 358 (dd, 1H); 3.32 (d, 2H); 3.03 (t, 2H); 2.95 (t, 2H); 2.78 (m, 2H); 1.82-1.60 (overlapping multiplets, 6H); 1.48 (m, 1H); 1.38 (m, 2H); 1.13 (m, 2H); 0.85 (t, 3H).



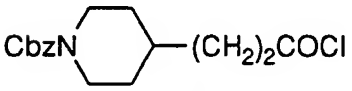
6-10



6-11



6-12



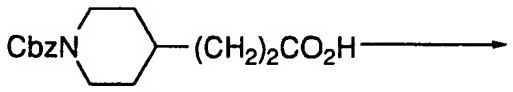
6-2

3-(4-N-Cbz-Piperidinyl)propanol (6-11)

Commercially available 4-pyridinepropanol (6-10) (38 g, 277 mmol) was dissolved in 100 ml EtOH/HOAc/H_2O (4:1:1) and treated with 2.0 g 10% Pd/C. This mixture was hydrogenated on a Parr reactor for 24 h at 55 psi. The catalyst was removed by filtration and the filtrate evaporated to give 3-(4-piperidinyl)propyl acetate. ^1H NMR ($CDCl_3$) δ 3.65 (t, 2H); 3.52 (d, 2H); 2.81 (t, 2H); 1.75 (d, 2H); 1.72 (m, 2H); 1.42 (m, 1H); 1.15 (m, 2H); 1.08 (m, 2H).

A mixture containing this acetate (21.5 g, 107 mmol), $NaHCO_3$ (17.56 g, 208 mmol), 100 ml H_2O, and 50 ml CH_2Cl_2 was vigorously stirred in a 500 ml flask. To this mixture benzyl chloroformate (16.76 ml, 117 mmol) in 50 ml of CH_2Cl_2 was added dropwise over a period of 1 h. The resulting mixture was stirred rapidly for 18 h then the organic phase was removed and the aqueous phase extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were dried over Na_2SO_4, filtered, concentrated, and purified by chromatography on silica (1:1 hexane/ethyl acetate) to give 6-11 as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H); 5.12 (s 2H); 4.09 (d, 2H); 3.65 (t, 2H); 2.81 (t, 2H); 1.84 (d, 2H); 1.72 (m, 2H); 1.42 (m, 1H); 1.21 (m, 2H); 1.08 (m, 2H).

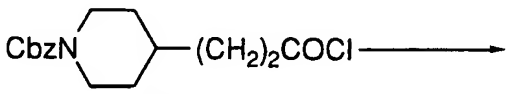


6-12

3-(4-N-Cbz-Piperidinyl)propionic acid (6-12)

6-11 (21.0 g, 73.0 mmol) was dissolved in 50 ml acetone and cooled to 0°C in an ice bath. Next, a solution of 2.67 M Jones reagent (41 ml, 109.5 mmol) was added dropwise over 1h and the mixture stirred for an additional 1h after the addition was completed. The excess oxidant was consumed by adding 10 ml of isopropanol and the insoluble precipitate dissolved by the addition of 150 ml of H_2O. The acetone was evaporated at reduced pressure and the aqueous residue extracted with Et_2O (3 x 100 ml). The combined Et_2O layers were extracted with sat. $NaHCO_3$ (2 x 50 ml), the basic extracts acidified with conc. HCl and extraced with CH_2Cl_2 (2 x 60 ml). The organic extracts were dried (Na_2SO_4) and evaporated yielding 6-12 as a colorless viscous oil.

^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H); 5.12 (s, 2H); 4.09 (d, 2H); 2.81 (t, 2H); 2.42 (t, 2H); 1.84 (d, 2H); 1.72 (t, 2H); 1.42 (m, 1H); 1.08 (m, 2H).

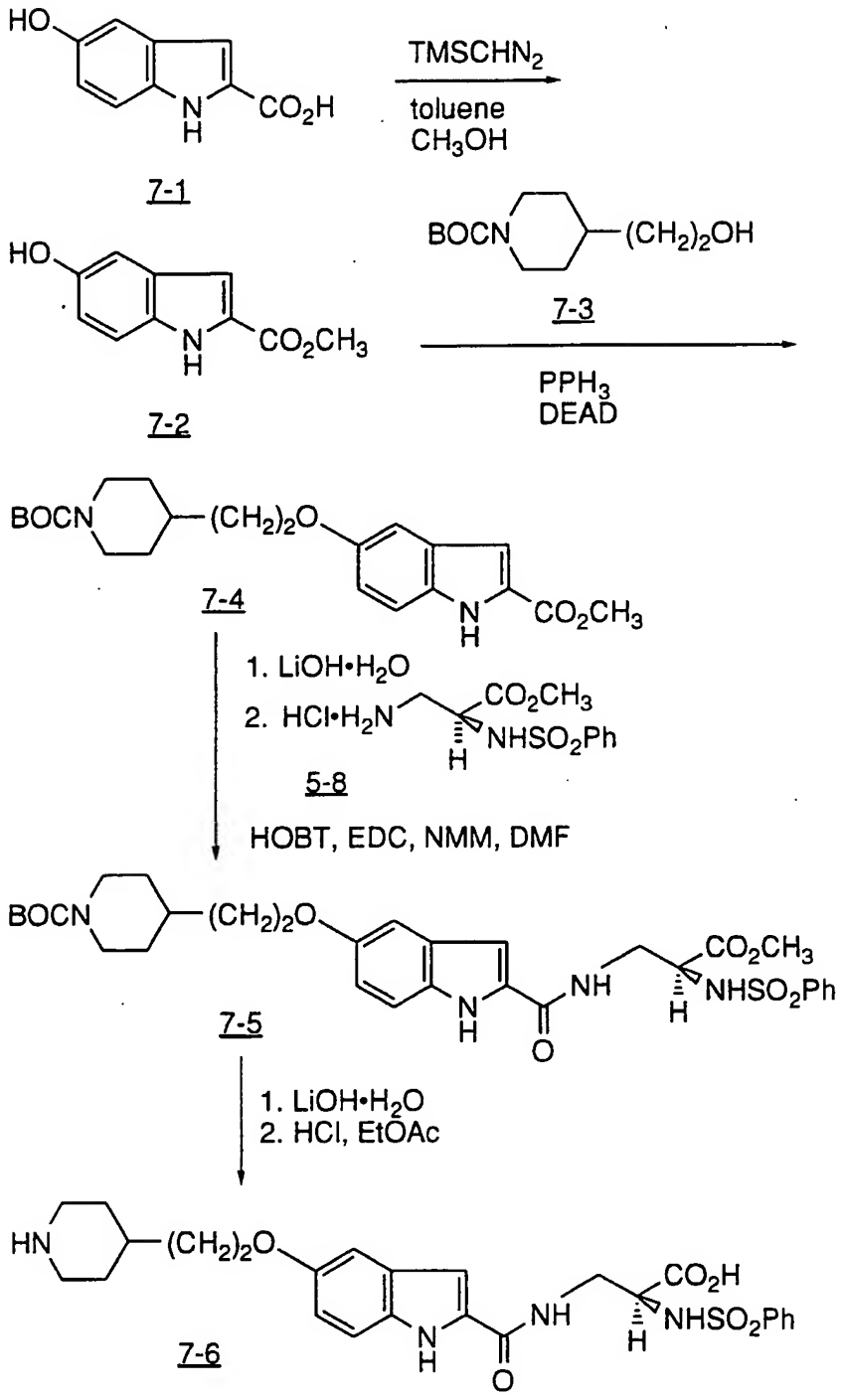


6-2

3-(4-N-Cbz-Piperidinyl)carbonyl chloride (6-2)

6-12 (3.0 g, 10.2 mmol) in 10 ml CH_2Cl_2 was treated with oxalyl chloride (1.33 ml, 15.3 mmol) the resulting mixture was stirred at room temperature for 1h then evaporated at reduced pressure and placed on a high vacuum line for 18h giving 6-2 as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H); 5.12 (s, 2H); 4.18 (d, 2H); 2.93 (t, 2H) 2.75 (t, 2H); 1.75-1.69 (m, 4H); 1.43 (m, 1H); 1.08 (m, 2H).

SCHEME 7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CO2H
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toluene
CH3OH
7-1
BOCN
(CH2)2OH
7-3
HO
N
H
CO2CH3
PPh3
DEAD
7-2
BOCN
(CH2)2O
N
H
CO2CH3
7-4
1. LiOH•H2O
2. HCl•H2N
CO2CH3
NHSO2Ph
H
5-8
HOBT, EDC, NMM, DMF
BOCN
(CH2)2O
N
H
NH
O
CO2CH3
NHSO2Ph
H
7-5
1. LiOH•H2O
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HN
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N
H
NH
O
CO2H
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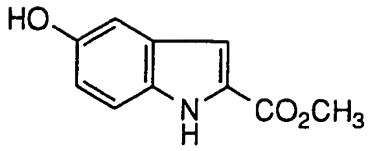
H
7-6

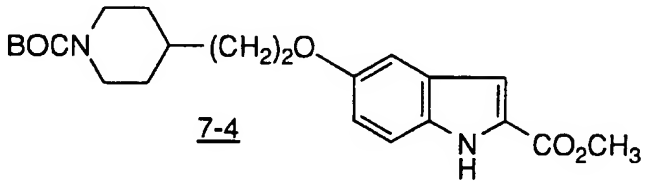


7-2

5-Hydroxy-2-indolecarboxylic acid methyl ester (7-2)

5-Hydroxyindole-2-carboxylic acid (Aldrich) (3.54 g, 0.02 mol) in toluene (100 ml)/methanol (25 ml) was treated with $TMSCHN_2$ (0.022 mol) and this solution was stirred at room temperature for 16 hours. The solvent was removed and the residue purified by flash chromatography on silica gel eluting with $CHCl_3$ (95)/MeOH(S) to give pure 7-2, R_f 0.3, silica, $CHCl_3$ (95)/MeOH(5).

^1H NMR (300 MH_3, $CDCl_3$) δ 3.94 (3H, S), 4.79 (1H, S), 6.94 (1H, dd), 7.09 (2H, m), 7.28 (1H, m), 8.82 (1H, b).

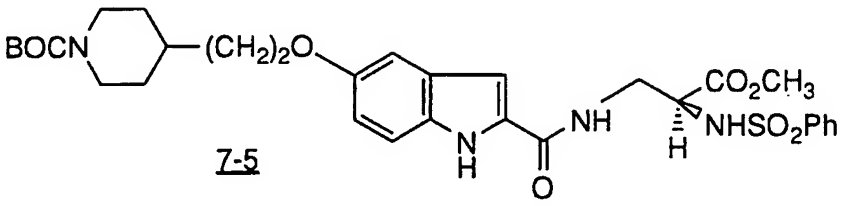


7-4

5-[2-(4-N-BOC-Piperidinylethyl)oxy]-2-indolecarboxylicacid methyl ester (7-4)

A solution of 7-2 (0.96 g, 5 mmol) in THF (15 ml) was treated with PPh_3 (1.48 g, 5.5 mmol) and after stirring for 10 minutes, diethyl azodicarboxyate (DEAD) (0.96 g, 5.5 mmol) in THF (10 ml) was added dropwise over 1 hour. After stirring at room temperature for 16 hours, the solvent was removed and the residue was taken up in EtOAc, washed with H_20, saturated $NaHCO_3$, brine, 10% $KHSO_4$, brine and dried (Na_2SO_4). The solvent was removed and the residue purified by flash chromatography on silica gel eluting with hexane(4)/EtOAc(1) to give pure 7-4.

^{1}H NMR (300 MH$_3$. CDCl$_3$) δ 1.20 (2H, m), 1.45 (9H, s), 1.59 (1H, s), 1.77 (4H, m), 2.71 (2H, bt), 3.92 (3H, s), 4.06 (3H, m), 6.98 (1H, dd), 7.07 (1H, m), 7.12 (1H, m), 7.31 (1H, d).



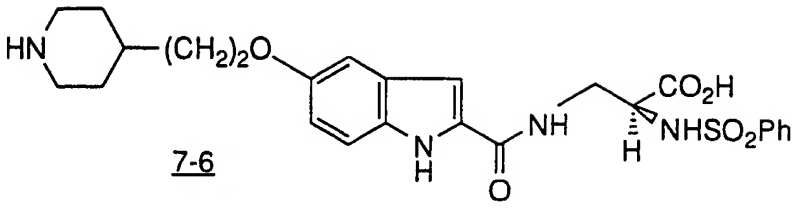
7-5

5-[2-(4-N-BOC-Piperidinylethyl)oxy]-2-indolecarbonyl-2(S)-phenyl-sulfonylamino-β-alanine (7-5)

7-4 (0.77 g, 1.9 mmol) was treated with LiOH•H$_2$O (0.24 g, 5.7 mmol) as described for 4-1 to give the desired acid. R$_f$ 0.5, silica, CHCl$_3$ (95)/MeOH(5).

This acid (0.226 g, 0.58 mmol) was dissolved in DMF and a room temperature was treated successively with 5-8 (0.17 g, 5.8 mmol), HOBT (0.086 g, 0.64 mmol), NMM (0.176 g, 1.74 mmol), and EDC (0.13 g, 0.68 mmol). After stirring for 24 hours, the solvent was removed and the residue was taken up in H$_2$O (50 ml)/EtOAc(100 ml) and this organic phase was washed with 10% KHSO$_4$, brine, saturated NaHCO$_3$, brine and dried (Na$_2$SO$_4$). The solvent was removed and the residue purified by flash chromatography on silica gel eluting with CHCl$_3$(95)/MeOH(5) to give pure 7-5.

^{1}H NMR (300 MH$_3$, CD$_3$OD) δ 1.13 (2H, m), 1.45 (9H, s), 1.73 (4H, m), 2.77 (2H, bt), 3.49 (3H, s), 3.57 (1H, m), 3.68 (1H, m), 4.03 (3H, m), 4.22 (1H, m), 6.89 (2H, m), 7.04 (1H, m), 7.30-7.43 (4H, m), 7.80 (2H, m).



7-6

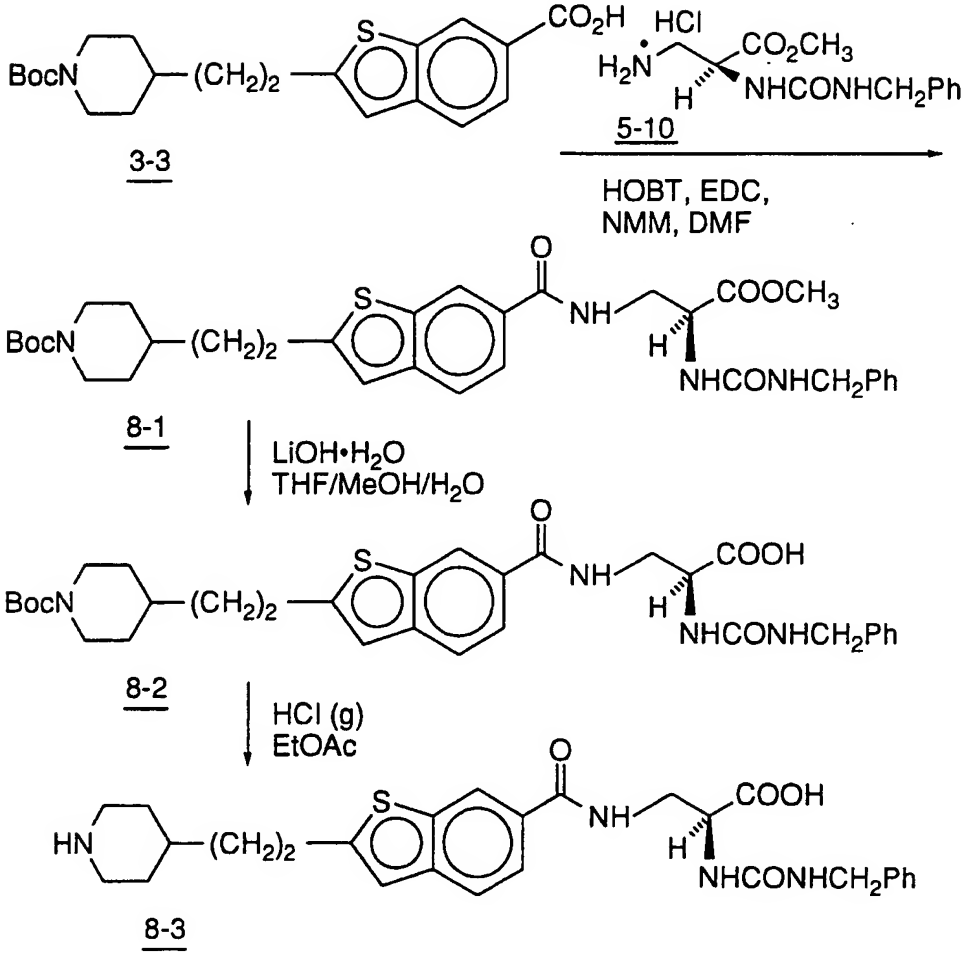
5-[2-(4-Piperidinylethyl)oxy]-2-indolecarbonyl-2(S)-phenylsulfonyl-amino-β-alanine (7-6)

7-5 (0.33 g, 0.53 mmol) was treated with $LiOH \cdot H_2O$ (0.066 g, 1.57 mmol) as described for 4-1 to provide the desired acid. R_f 0.1, silica $CHCl_3$ (95)/CH_3OH(5)/HOAc(1).

This acid was dissolved in EtOAc, cooled to -25° and treated with HCl gas as described for 4-3 to give pure 7-6.

^1H NMR (300 MH_3, CD_3OD) δ 1.48 (2H, m), 1.80 (2H, m), 1.90-2.08 (3H, m), 3.00 (2H, dt), 3.39 (2H, d), 3.54 (1H, m), 3.73 (1H, dd), 4.08 (2H, m), 4.19 (1H, m), 6.88 (2H, m), 7.09 (1H, m), 7.36 (4H, m), 7.82 (2H, m).

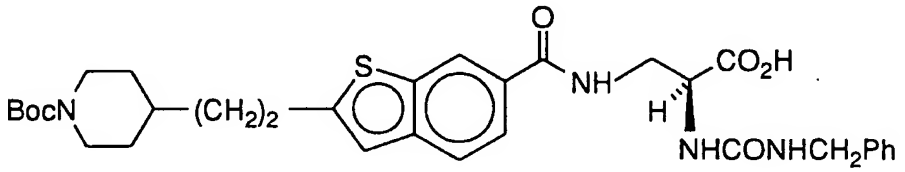
SCHEME 8


BocN
(CH2)2
S
CO2H
3-3
HCl
H2N
CO2CH3
H
NHCONHCH2Ph
5-10
HOBT, EDC,
NMM, DMF
O
NH
COOCH3
8-1
LiOH•H2O
THF/MeOH/H2O
COOH
8-2
HCl (g)
EtOAc
HN
8-3

2-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]benzothiophene-6-N-[3-(Methyl-2(S)-benzyureidopropionate]carboxamide (8-1)

A solution of 3-3 (0.234g, 0.0006 mol.), 2-15 (0.173 g, 0.0006 mol.) and HOBT (0.089 g, 0.00066 mol) in DMF (20 ml) was treated with NMM (0.182 g, 0.0018 mol) and EDC (0.144 g, 0.00075 mol) as described for 4-1 to give 8-1 Rf 0.46, silica, $CHCl_3$ (95)/MeOH (S).

^1H NMR (300 MHZ, $CDCl_3$) δ 1.07-1.23 (2H, m), 1.47 (9H, s), 1.60-1.80 (4H, m), 2.57-2.75 (2H, bt), 2.85-3.0 (2H, t), 3.71 (3H, s), 3.73-3.90 (2H, bm), 4.00-4.18 (2H, bd), 4.29 (2H, s), 4.67-4.80 (1H, t), 5.40-6.50 (2H, vb), 7.00 (1H, s), 7.10-7.23 (5H, bs) 7.47-7.72 (3H, m), 8.20 (1H, s).

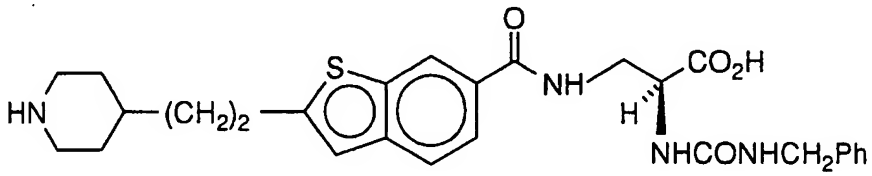


8-2

2-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-benzylureidopropionic acid)]carboxamide (8-2)

8-1 (0.209 g, 0.000326 mole) was treated with $LiOH \cdot H_2O$ as described for 2-5 to give 8-2.

^1H NMR (300 MHZ, $CDCl_3$) δ 1.04-1.25 (2H, m), 1.45-1.60 (1H, m), 1.45 (9H, s), 1.60-1.82 (4H, m), 2.56-2.76 (2H, bt), 2.80-3.00 (2H, t), 3.68-3.95 (2H, m), 3.97-4.32 (4H, m), 4.46-4.60 (1H, b), 6.00-6.40 (1H, b), 6.60-6.85 (1H, b), 6.94 (1H, s), 7.00-7.23 (5H, m), 7.50-7.67 (2H, dd) 7.70-7.85 (1H, b), 8.14 (1H, s).



8-3

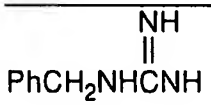
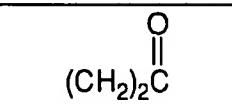
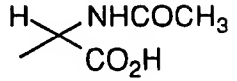
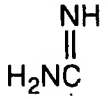
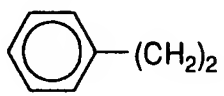
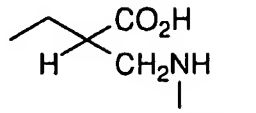
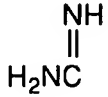
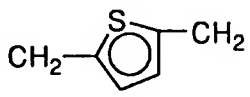
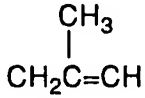
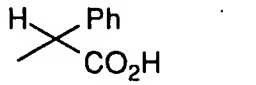
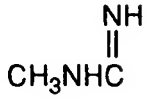
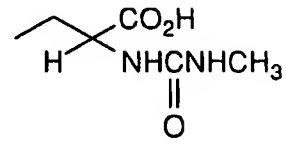
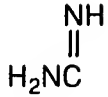
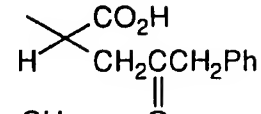
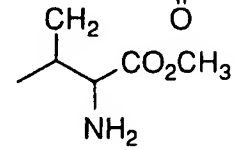
2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-benzylureido-propionic acid]carboxamide (8-3)

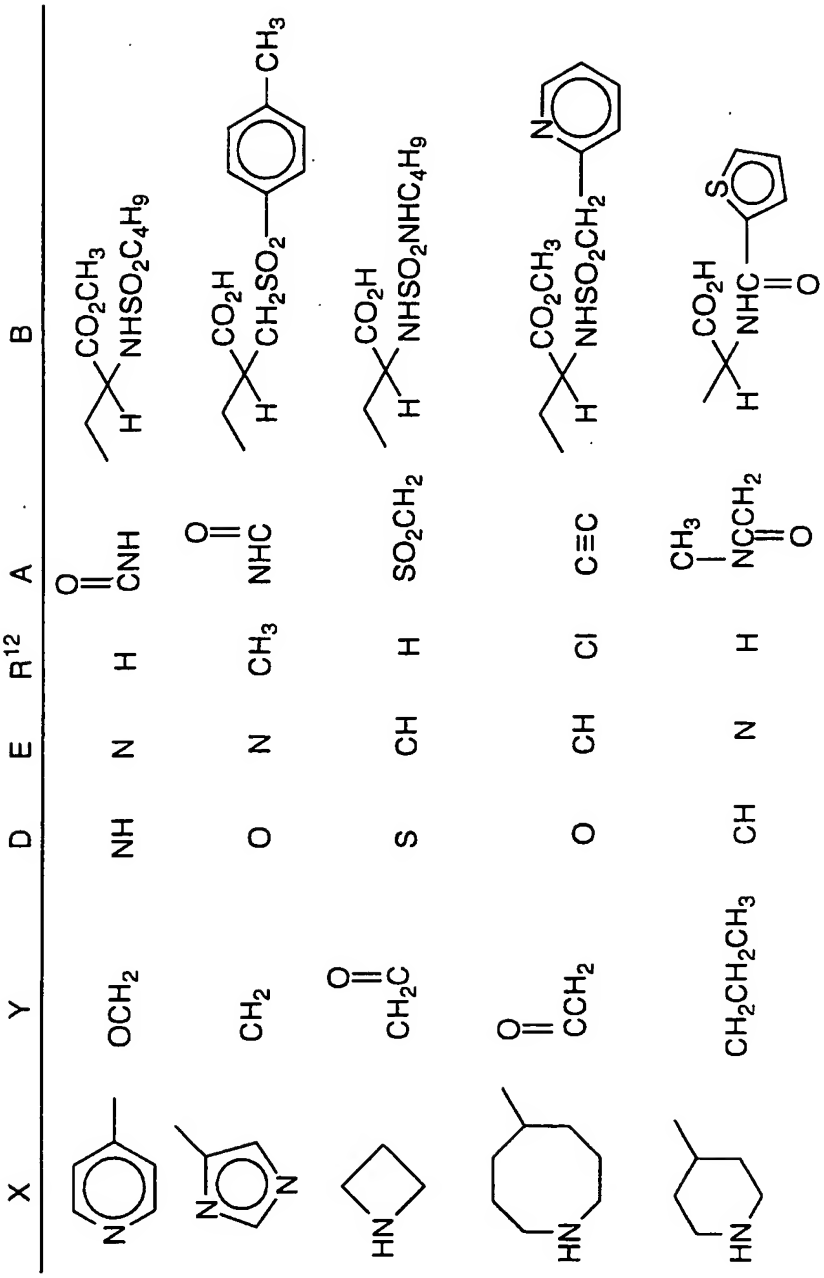
8-2 was suspended in EtOAc and treated with HCl (g) as described for 3-5 to give 8-3. Rf 0.52, silica, EtOH(10)/-H_2O(1)/-NH_4OH (1).

^1H NMR (300 MHz, CD_3OD) δ 1.45-1.55 (2H, m) 1.62-1.94 (3H, m), 1.96-2.12 (2H, 6d), 2.88-3.12 (4H, m), 3.30-3.45 (2H, m), 3.70-3.85 (2H, t), 4.20-4.37 (2H, q), 4.58-4.67 (1H, dd), 7.02-7.25 (6H, m), 7.72 (2H, s), 8.25 (1H, s).

In addition to those compounds specifically exemplified above, additional compounds of the present invention are set forth in tabular form below. These compounds are synthesized by use of the synthetic routes and methods described in the above Schemes and Examples and variations thereof well known to those of ordinary skill in the art, and not requiring undue experimentation. All varibles listed in the Tables below are with reference to the following generic structure:

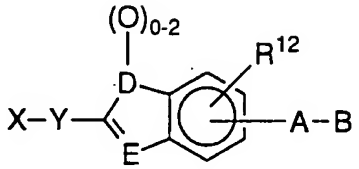
X	Y	D	E	R^{12}	A	B
CH_3NH	$(CH_2)_5SO_2$	O	N	CH_3	$\overset{O}{\overset{\|}{C}}NH$	
	$(CH_2)_3O$	S	N	F	$\overset{O}{\overset{\|}{C}}N(CH_3)$	
	$(CH_2)_2OCH_2$	CH	O	CH_2CF_3	$CH=CH$	
	$CH_2SO_2(CH_2)_2$	CH	N	CH_2OCH_3	$C\equiv C$	

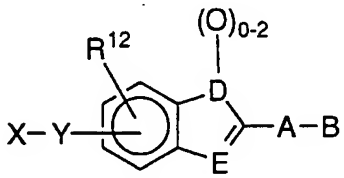
X	Y	D	E	R^{12}	A	B
		O	CH	CH_2CO_2Me	CH_2SO_2NH	
		S	CH	H		
		O	N	OC_2H_5		
	CH_2S	NH	N	H	$NHSO_2$	
	CH=CH	O	CH	Ph	CH_2	
H_2N	$(CH_2)_6$	CH	N	OCH_3	$C\equiv CH_2$	



WHAT IS CLAIMED IS:

1. A fibrinogen receptor antagonist of the following formula:





and pharmaceutically acceptable salts, where D and E are independently chosen from C, N, O and S;

X is chosen from:

$-NR^1R^2$, $-NR^1-\overset{\overset{NR^2}{\|}}{C}-R^1$, $-\overset{\overset{NR^3}{\|}}{C}-NHR^4$,

$-NR^1-\overset{\overset{NR^2}{\|}}{C}-NR^3R^4$, and a 5- to 6- membered mono- or bicyclic aromatic or nonaromatic ring system containing 0, 1, or 2 heteroatoms selected from N, O and S and either unsubstituted or substituted with R^1, R^2, R^3 or R^4, wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,

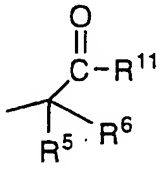
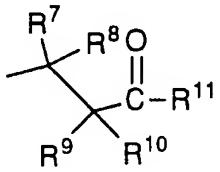
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy, and
hydroxy C_{0-6} alkyl;

Y and A are independently chosen from

$(CH_2)_m$, $(CH_2)_m\overset{O}{\overset{\|}{C}}NR_3(CH_2)_n$, $(CH_2)_mNR_3\overset{O}{\overset{\|}{C}}(CH_2)_n$, $(CH_2)_mO(CH_2)_n$
$(CH_2)_m\overset{O}{\overset{\|}{C}}(CH_2)_n$, $(CH_2)_m\overset{S}{\overset{\|}{C}}(CH_2)_n$, $(CH_2)_mSO_2(CH_2)_n$,
$(CH_2)_mS(CH_2)_n$, $(CH_2)_mSO(CH_2)_n$,
$(CH_2)_mSO_2NR_3(CH_2)_n$, $(CH_2)_mNR_3SO_2(CH_2)$,
$(CH_2)_mCR_3{=}CR_4(CH_2)_n$, $(CH_2)_mC{=}C(CH_2)_n$,
$(CH_2)_mCH(CH_2)_n$, and $(CH_2)_m$aryl$(CH_2)_n$,
$(CH_2)_mNR_3(CH_2)_n$,
OH
and $(CH_2)_mNR_3(CH_2)_n$,

where m and n are integers independently chosen from 0-6;

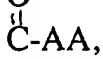
B is chosen from


and


where R_5, R_6, R_7, R_8, R_9, and R_{10} are independently chosen from:
hydrogen, flourine, C_{1-8} alkyl, hydroxyl,

hydroxy C_{1-6} alkyl, carboxy C_{0-6} alkyl,
C_{1-6} alkyloxy, C_{3-8} cycloalkyl, aryl C_{1-6} alkyloxy,
aryl C_{0-6} alkyl, C_{1-6} alkylcarbonyloxy,
C_{0-6} alkylamino C_{0-6} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
C_{0-6} dialkylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyloxy,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
aryl C_{0-6} alkylaminocarbonyloxy,
aryl C_{0-8} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonyl C_{0-6} alkyl, and
aryl C_{0-8} alkylaminocarbonyl C_{0-6} alkyl,

wherein groups may be unsubstituted or substituted with one or more selected from R^1 and R^2; and

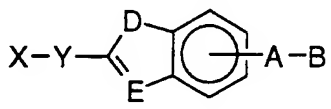

C-AA, where AA is an L- or D-amino acid, or its corresponding ester, connected through an amide linkage;

R^{11} is chosen from:

hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy, and
an L- or D- amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C_{1-6} alkyl; and

R^{12} is chosen from the group described by R^1.

2. A compound of Claim 1 having the formula



and pharmaceutically acceptable salts, where D and E are independently chosen from O, N, C and S;

X is chosen from:

$-NR^1R^2$, $-NR^1-\overset{\overset{NR^2}{\|}}{C}-R^1$, $-\overset{\overset{NR^3}{\|}}{C}-NHR^4$,

$-NR^1-\overset{\overset{NR^2}{\|}}{C}-NR^3R^4$, or a 5- to 6- membered mono- or bicyclic nonaromatic ring system containing 0, 1, or 2 heteroatoms selected from N, O, and S and either unsubstituted or substituted with R^1, R^2, R^3 and R^4, wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen,

C_{1-10} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,

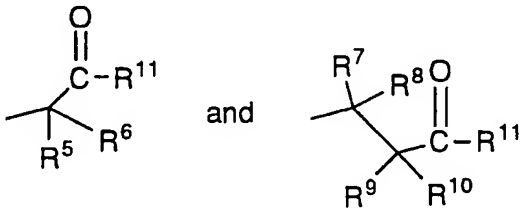
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

Y and A are independently chosen from:

$(CH_2)_m$, $(CH_2)_m\overset{O}{\overset{\|}{C}}NR^3(CH_2)_n$, $(CH_2)_mNR^3\overset{O}{\overset{\|}{C}}(CH_2)_n$,
$(CH_2)_mO(CH_2)_n$, $(CH_2)_mS(CH_2)_n$, $(CH_2)_mSO_2NR^3(CH_2)_n$,
and $(CH_2)_mCR^3{=}CR^4(CH_2)_n$, $(CH_2)_mNR^3(CH_2)_n$

where m and n are integers independently chosen from 0-6;

B is chosen from:



where R^5, R^6, R^7, R^8, R^9, and R^{10} are independently chosen from:
hydrogen, flourine, C_{1-8} alkyl, hydroxyl,
hydroxy C_{1-6} alkyl, carboxy C_{0-6} alkyl,C_{1-6} alkyloxy,
C_{3-8} cycloalkyl, aryl C_{0-6} alkyl,
C_{1-6} alkylcarbonyloxy, C_{0-6} alkylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyloxy,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
aryl C_{1-6} alkylaminocarbonyloxy,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,

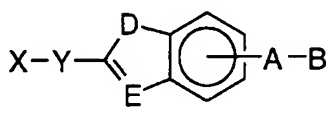
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl, and
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl,

wherein groups may be unsubstituted or substituted with one or more selected from R^1 and R^2; and

C-AA, where AA is an L- or D-amino acid, or its corresponding ester, connected through an amide linkage; and

R^{11} is chosen from:
hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy, and
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy, and
an L- or D- amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C_{1-6} alkyl.

3. A compound of Claim 2 having the formula



and pharmaceutically acceptable salts where D and E are independently chosen from C, N, O or S;

X is chosen from:

$-NR^1R^2$, $-\overset{\overset{NR3}{\|}}{C}-NHR^4$, and a 5- to 6- membered mono- or bicyclic nonaromatic ring system containing 0, 1, or 2 heteroatoms selected from N, O, and S and either unsubstituted or substituted with R^1, R^2, R^3 and R^4, wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{1-4} alkoxy C_{0-6} alkyl;

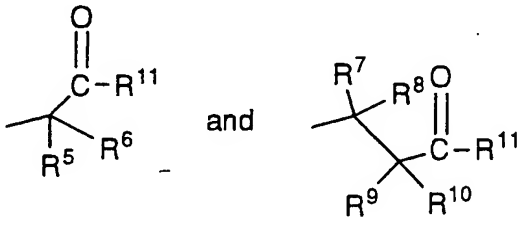
Y and A are optional substituents that are independently chosen from:

$(CH_2)_m$, $(CH_2)_m\overset{O}{\overset{\|}{C}}NR3(CH_2)_n$, $(CH_2)_mNR3\overset{O}{\overset{\|}{C}}(CH_2)_n$,

$(CH_2)_mO(CH_2)_n$, $(CH_2)_m\overset{O}{\overset{\|}{C}}(CH_2)_n$, $(CH_2)_mSO_2(CH_2)_n$, and $(CH_2)_mSO_2NR3(CH_2)_n$,

where m and n are integers independently chosen from 0-6;

B is chosen from:



where R^7, R^8, R^9, and R^{10} are independently chosen from:

hydrogen, flourine,

C_{1-8} alkyl, hydroxyl, hydroxy C_{1-6} alkyl,

carboxy C_{0-6} alkyl,C_{1-6} alkyloxy,
C_{3-8} cycloalkyl, aryl C_{0-6} alkyl, C_{1-6} alkylcarbonyloxy,
C_{0-6} alkylamino C_{0-6} alkyl, aryl C_{0-6} alkylcarbonyloxy,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alykl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl, and
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl; and

R^{11} is chosen from:
hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy.

4. A compound of claim 3 selected from the group consisting of:

2-(Butylsulfonylamino)-3-{5[2'-(4-piperidin-4-yl-propyl)benzofuranyl]}propanoic acid;
2-(Butylsulfonylamino)-3-{5-[2'-(4-piperidin-4-yl-methyl)aminocarbonyl]benzofuranyl}propionic acid;
2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-N-carbobenzyloxyaminopropionic acid)carboxamide;

2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2(S)-N-butyl-sulfonylaminopropionic acid)carboxamide;
2-[2-(Piperidin-4-yl)ethyl]benzothiophene-S,S-dioxide-6-N-[3-(2(S)-N-butylsulfonylaminopropionic acid)carboxamide;
2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2-(S)-N-Methylsulfonylaminopropionic acid)]carboxamide;
2-[2-(4-Piperidinyl)ethyl]benzimidazole-5-carbonyl-[2(S)-p-toluenesulfonylamino]-ß-alanine;
2-[2-(4-Piperidinyl)ethyl]benzimidazole-5-carbonyl-[2(S)-butylsulfonylamino]-ß-alanine;
5-[2-[4-Piperidinylethyl)oxy]-2-indolecarbonyl-2(S)-phenylsulfonylamino-ß-alanine; and
2-[2-(Piperidin-4-yl)ethyl]benzothiophene-6-N-[3-(2-(S)-benzylureido)propionic acid]carboxamide, and
and pharmaceutically acceptable salts thereof.

5. A compound of Claim 1 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.

6. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

7. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

8. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 1 in combination with a thrombolytic agent and a pharmaceutically acceptable carrier.

9. The composition of Claim 8 wherein the thrombolytic agent is a plasminogen activator or streptokinase.

10. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 1 in combination with an anticoagulant and pharmaceutically acceptable carrier.

11. The composition of Claim 10, wherein the anticoagulant is heparin or warfarin.

12. A composition for preventing thrombus or embolus formation in a mammal, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

13. A composition for preventing thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with a thrombolytic agent and a pharmaceutically acceptable carrier.

14. The composition of Claim 13, wherein the thrombolytic agent is plasminogen activator or streptokinase.

15. A composition for preventing thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with an anticoagulant and pharmaceutically acceptable carrier.

16. The composition of Claim 15 wherein the anticoagulant is heparin or warfarin.

17. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

18. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with a thrombolytic agent and a pharmaceutically acceptable carrier.

19. The composition of Claim 18, wherein the thrombolytic agent is plasminogen activator or streptokinase.

20. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with an anticoagulant and pharmaceutically acceptable carrier.

21. The composition of Claim 20, wherein the anticoagulant is heparin or warfarin.

22. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with an antiplatelet agent and a pharmaceutically acceptable carrier.

23. The composition of Claim 22, wherein the antiplatelet agent is aspirin.

24. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 7.

25. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 7.

26. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 8.

27. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 10.

28. A method for preventing thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 12.

29. A method for preventing thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 13.

30. A method for preventing thrombus or embolus formation in a mammal, comprising administering to the mammal the composition Claim 15.

31. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 17.

32. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 18.

33. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 20.

34. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 22.

35. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 1 in combination with two or more agents selected from a thrombolytic agent, an anticoagulant agent, and an antiplatelet agent and a pharmaceutically acceptable carrier.

36. The composition of Claim 35, wherein the thrombolytic agent is a plasminogen activator or streptokinase, the anticoagulant agent is heparin or warfarin, and the antiplatelet agent is aspirin.

37. A composition for preventing or treating thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with two or more agents selected from a thrombolytic agent, an anticoagulant agent, and an antiplatelet agent and a pharmaceutically acceptable carrier.

38. The composition of Claim 37, wherein the thrombolytic agent is a plasminogen activator or streptokinase, the anticoagulant agent is heparin or warfarin, and the antiplatelet agent is aspirin.

39. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 35.

40. A method for preventing or treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 37.

41. A compound of Claim 2 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.

42. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

43. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

44. A composition for preventing thrombus or embolus formation in a mammal, comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

45. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

46. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 43.

47. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 43.

48. A method for preventing thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 44.

49. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 45.

50. A compound of Claim 3 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.

51. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 3 and a pharmaceutically acceptable carrier.

52. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 3 and a pharmaceutically acceptable carrier.

53. A composition for preventing thrombus or embolus formation in a mammal, comprising a compound of Claim 3 and a pharmaceutically acceptable carrier.

54. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 3 and a pharmaceutically acceptable carrier.

55. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 52.

56. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 52.

57. A method for preventing thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 53.

58. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 54.

59. A compound of Claim 4 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.

60. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 4 and a pharmaceutically acceptable carrier.

61. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 4 and a pharmaceutically acceptable carrier.

62. A composition for preventing thrombus or embolus formation in a mammal, comprising a compound of Claim 4 and a pharmaceutically acceptable carrier.

63. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 4 and a pharmaceutically acceptable carrier.

64. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 61.

65. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 61.

66. A method for preventing thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 62.

67. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 63.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09730

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, APS IMAGE, DIALOG,
search terms: structure, fibrinogen?()recept? and (antagonist? or inhibit?)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	Chemical Abstract, Vo. 118, No. 2, issued 11 January 1993; Himmelsbach, F. et al. "preparation of cyclic ureas as cell-cell and cell-matrix interaction inhibitors" Abst. No. 118:101980e	1-3
A,P	US, A, 5,227,490, (HARTMAN et al.) 13 JULY 1993, see entire document.	1-67
A	EP, A, 0,384,362 (Alig, L. et al.) 29 AUGUST 1990, see entire document.	1-67
A	EP, A, 0,478,362, (DUGGAN, M. et al.) 01 APRIL 1992, see entire document.	1-67

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 NOVEMBER 1993	DEC 28 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer CELIA CHANG
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-4702

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09730

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A, 0,479,481, (DUGGAN, M. et al.) 08 APR 1992, see entire document	1-67

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09730

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

C07D 205/00, 225/00. 491/048, 493/06, 495/06, 498/06, 513/06;
A61K 31/33, 31/34, 31/38, 31/395, 31/415, 31/42, 31/425, 31/44, 31/445;

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/183, 210, 318, 320, 321, 322, 323,324, 337, 338, 339, 367, 375, 394, 395, 397, 443, 469, 470;
540/200, 483; 546/193, 195, 197, 198, 199, 201, 202, 209, 270, 271, 273, 274; 548/161, 163, 165, 171, 178, 179, 180, 221, 222, 304.4, 304.7, 306.1, 306.4, 307.1, 307.4, 308.4, 309.7, 517, 518, 530, 537, 540; 549/49, 57, 58, 462, 466, 467, 468;

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/183, 210, 318, 320, 321, 322, 323,324, 337, 338, 339, 367, 375, 394, 395, 397, 443, 469, 470;
540/200, 483; 546/193, 195, 197, 198, 199, 201, 202, 209, 270, 271, 273, 274; 548/161, 163, 165, 171, 178, 179, 180, 221, 222, 304.4, 304.7, 306.1, 306.4, 307.1, 307.4, 308.4, 309.7, 517, 518, 530, 537, 540; 549/49, 57, 58, 462, 466, 467, 468;